

## **20. APPENDICES TO THE PBRER**

**20.1. Appendix 1 Reference Safety Information**

CCDS v11.0 dated 10 Dec 2021

**Moderna COVID-19 Vaccine**  
**COMPANY CORE DATA SHEET**  
**CCDS0001/10 December 2021/Version 11.0**

IMPORTANT NOTE: Grey highlight text is mandatory for all regional Prescribing Information

## **1. NAME OF THE MEDICINAL PRODUCT**

SPIKEVAX

Pharmaceutical form: 0.20 mg/mL dispersion for injection

INN: elasomeran

Common name assigned by EU: COVID-19 mRNA Vaccine (nucleoside modified)

## **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

One dose (0.5 mL) of the primary series contains 100 micrograms of messenger RNA (mRNA) (embedded in SM-102 lipid nanoparticles).

One dose (0.25 mL) of the booster contains 50 micrograms of messenger RNA (mRNA) (embedded in SM-102 lipid nanoparticles).

Single-stranded, 5'-capped messenger RNA (mRNA) produced using cell-free in vitro transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2 embedded in the SM-102 lipid nanoparticles [composed of the lipids, Heptadecan-9-yl 8-((2-hydroxyethyl) (6-oxo-6-(undecyloxy) hexyl) amino)octanoate (SM-102)].

Moderna COVID-19 Vaccine does not contain any preservatives, antibiotics, adjuvants, or human- or animal-derived materials. The vial stopper does not contain natural rubber latex.

For the full list of excipients, see section 6.1.

## **3. PHARMACEUTICAL FORM**

Dispersion for injection

White to off white dispersion (pH: 7.0 – 8.0).

Alternate description of pharmaceutical form is “Suspension for injection”. The pharmaceutical form on the prescribing information should align with the description on the carton.

## **4. CLINICAL PARTICULARS**

### **4.1 Therapeutic indications**

Moderna COVID-19 Vaccine is indicated for active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 in individuals 6 years of age and older.<sup>1</sup>

## **4.2 Posology and method of administration**

### Posology

#### ***Primary series***

##### *Individuals 12 years of age and older*

Moderna COVID-19 Vaccine (100 micrograms, 0.5 mL) is a two-dose regimen.

##### *Individuals 6 through 11 years of age*

Moderna COVID-19 Vaccine is administered as a course of 2 (two) 50 microgram doses (0.25 mL each).<sup>2</sup>

The second dose should be administered one month after the first dose (see sections 4.4 and 5.1).

##### *Immunocompromised individuals*

A third dose of the Moderna COVID-19 Vaccine (0.5 mL) administered at least 28 days following the first two doses of this vaccine is authorised for administration to individuals at least 18 years of age who have undergone solid organ transplantation, or who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise.

#### ***Booster dose***

##### *Individuals 18 years of age and older*

Moderna COVID-19 Vaccine is administered intramuscularly as a single dose (0.25 mL) at least 6 months after completing a primary series.<sup>3</sup>

#### ***Interchangeability***

##### *Primary series*

The interchangeability of Moderna COVID-19 Vaccine with other COVID-19 vaccines to complete the primary vaccination course has not been established.

Individuals who have received one dose of Moderna COVID-19 Vaccine (0.5 mL, 100 micrograms) should receive a second dose of Moderna COVID-19 Vaccine (0.5 mL, 100 micrograms) to complete the primary vaccination course.

Children aged 6 through 11 years who have received one dose of Moderna COVID-19 Vaccine (0.25 mL, 50 micrograms) should receive a second dose of Moderna COVID-19 Vaccine (0.25 mL, 50 micrograms) to complete the primary vaccination course.

##### *Booster dose in individuals 18 years of age and older*

A single booster dose of the Moderna COVID-19 Vaccine (0.25 mL) may be administered as a heterologous booster dose following completion of primary vaccination with another authorised or approved COVID-19 vaccine. The eligible population(s) and dosing interval for the



heterologous booster dose are the same as those authorised for a booster dose of the Moderna COVID-19 Vaccine.

### ***Paediatric population***

The safety and efficacy of Moderna COVID-19 Vaccine in children and adolescents less than 6 years of age have not yet been established. No data are available.

### ***Elderly population***

Clinical studies of Moderna COVID-19 Vaccine included participants 65 years of age and older receiving vaccine or placebo, and their data contribute to the overall assessment of safety and efficacy. In the ongoing adult study of primary series dosing (0.5 mL), 24.8% (n=7,520) of participants were 65 years of age and older and 4.6% (n=1,399) of participants were 75 years of age and older. Vaccine efficacy in participants 65 years of age and older was 86.4% (95% CI 61.4, 95.2) compared to 95.6% (95% CI 90.6, 97.9) in participants 18 to <65 years of age. Overall, there were no notable differences in the safety profiles observed in participants 65 years of age and older and younger participants.

In the ongoing clinical study of a single booster dose (0.25 mL), 22.2% (n=38) of participants were 65 years of age and older. This study did not include sufficient numbers of participants 65 years of age and older to determine whether they respond differently than younger participants. Some local and systemic adverse reactions were reported in a lower proportion of participants 65 years of age and older compared to participants 18 through 64 years of age.

### **Method of administration**

The vaccine should be administered intramuscularly. The preferred site is the deltoid muscle of the upper arm.

Do not administer this vaccine intravascularly, subcutaneously or intradermally.

The vaccine should not be mixed in the same syringe with any other vaccines or medicinal products.

For precautions to be taken before administering the vaccine, see section 4.4.

For instructions regarding thawing, handling and disposal of the vaccine, see section 6.6.

## **4.3 Contraindications**

Moderna COVID-19 Vaccine is contraindicated in individuals with known severe allergic reactions (e.g., anaphylaxis) to any component of the vaccine or to a previous dose of Moderna COVID-19 Vaccine. See excipients listed in 6.1.

## **4.4 Special warnings and precautions for use**

### **Hypersensitivity and anaphylaxis**

Anaphylaxis has been reported in individuals who have received the Moderna COVID-19 Vaccine. Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following the administration of the vaccine.

Close observation is recommended following vaccination as follows:

- 30 minutes:
  - People with a history of an immediate allergic reaction of any severity to another vaccine or injectable therapy.
  - People with a history of anaphylaxis due to any cause.
- 15 minutes:
  - All other persons.

A second dose of the vaccine should not be given to those who have experienced anaphylaxis to the first dose of Moderna COVID-19 Vaccine.

### Myocarditis and pericarditis

There have been very rare reports of myocarditis and pericarditis occurring after vaccination with Moderna COVID-19 Vaccine. The majority of the cases have been reported in young males, and shortly after the second dose of the vaccine. These are typically mild cases and individuals tend to recover within a short time following standard treatment and rest.

Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis.

The risk of myocarditis after a third dose (0.5 mL, 100 micrograms) or booster dose (0.25 mL, 50 micrograms) of Moderna COVID-19 Vaccine has not yet been characterised.

### Altered immunocompetence

If Moderna COVID-19 Vaccine is administered to immunocompromised persons, including those receiving immunosuppressive therapy, the immune response to the vaccine may be diminished.

From an independent report (*Hall VG, Ferreira VH, Ku T et al. Randomized Trial of a Third Dose of mRNA-1273 Vaccine in Transplant Recipients. N Engl J Med*), safety and effectiveness of a third dose of the Moderna COVID-19 Vaccine have been evaluated in participants who received solid organ transplants. The administration of a third vaccine dose (0.5 mL) appears to be only moderately effective in increasing antibody titers. Patients should be counselled to maintain physical precautions to help prevent COVID-19. In addition, close contacts of immunocompromised persons should be vaccinated as appropriate for their health status.

### Persons at risk of bleeding

As with other intramuscular injections, Moderna COVID-19 Vaccine should be given with caution in individuals with bleeding disorders, such as haemophilia, or individuals currently on anticoagulant therapy, to avoid the risk of haematoma following the injection.

#### Acute illness

Consideration should be given to postponing immunisation in persons with severe febrile illness or severe acute infection. Persons with moderate or severe acute illness should be vaccinated as soon as the acute illness has improved.

#### Limitations of vaccine effectiveness

Vaccination with Moderna COVID-19 Vaccine may not protect all recipients.

#### Excipients with known effect

##### *Sodium*

This vaccine contains 0.033 mg of sodium per 0.5 mL dose and is considered ‘sodium-free’.

### **4.5 Interaction with other medicinal products and other forms of interaction**

#### Other vaccines

There are no data to assess the concomitant administration of Moderna COVID-19 Vaccine with other vaccines.

### **4.6 Fertility, pregnancy and lactation**

#### Pregnancy

No adequate and well-controlled studies of Moderna COVID-19 Vaccine use in pregnant women have been conducted. Available data on Moderna COVID-19 Vaccine administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy.

In a developmental toxicity study, 0.2 mL of a vaccine formulation containing the same quantity of mRNA (100 mcg) and other ingredients included in a single human dose of Moderna COVID-19 Vaccine was administered to female rats by the intramuscular route on four occasions: 28 and 14 days prior to mating, and on gestation days 1 and 13. No vaccine-related adverse effects on female fertility, foetal development or postnatal development were reported in the study.

## Breast-feeding

Data are not available to assess the effects of Moderna COVID-19 Vaccine on the breastfed infant or on milk production/excretion. Pregnant or breastfeeding mothers are advised to discuss their options with their healthcare providers.

## Fertility

No data are available on fertility in humans with use of Moderna COVID-19 Vaccine.

### **4.7 Effects on ability to drive and use machines**

No studies on the effects of the Moderna COVID-19 Vaccine on the ability to drive and use machines have been performed.

Some of the effects mentioned under section 4.8 “Undesirable Effects” may affect the ability to drive or use machines.

### **4.8 Undesirable effects**

#### Summary of the safety profile

##### *Participants 18 years of age and older*

The safety profile presented below is based on data generated in a placebo-controlled clinical study on 30,351 participants<sup>4</sup> ≥ 18 years of age.

Solicited adverse reactions were reported more frequently among vaccine participants than placebo participants. The most frequently reported adverse reactions after any dose in the vaccine group were pain at the injection site (92.0% any grade; 6.1% grade ≥ 3), fatigue (70.1% any grade; 10.1% grade ≥ 3), headache (64.9% any grade; 5.8% grade ≥ 3), myalgia (61.6% any grade; 9.1% grade ≥ 3) arthralgia (46.5%; 5.4% grade ≥ 3), and chills (45.5% any grade; 1.4% grade ≥ 3). The majority of local and systemic adverse reactions had a median duration of 1 to 3 days.

Overall, there was a higher reported rate of adverse reactions in adults aged 18 to < 65 years than in those aged 65 years and above.

Grade 3 solicited local adverse reactions were more frequently reported after Dose 2 than after Dose 1. In the participants who received the vaccine, solicited systemic adverse reactions were reported more frequently after Dose 2 than after Dose 1. Grade 3 systemic adverse reactions were reported more frequently after Dose 2 than after Dose 1.

##### *Immunocompromised participants 18 years of age and older*

From an independent report (Hall VG, Ferreira VH, Ku T et al. Randomized Trial of a Third

*Dose of mRNA-1273 Vaccine in Transplant Recipients. N Engl J Med*) in 60 participants who had undergone various solid organ transplant procedures (heart, kidney, kidney-pancreas, liver, lung, pancreas) a median of 3.57 years previously (range 1.99-6.75 years) who received a third vaccine dose, the adverse event profile was similar to that after the second dose and no grade 3 or grade 4 events were reported.

#### *Adolescents 12 through 17 years of age*

Safety data for Moderna COVID-19 Vaccine in adolescents were collected in an ongoing Phase 2/3 randomised, placebo-controlled, observer-blind clinical trial (Study 2, NCT04649151) conducted in the United States involving 3,726<sup>5</sup> participants 12 through 17 years of age who received at least one dose of Moderna COVID-19 Vaccine (n=2,486) or placebo (n=1,240). Overall, 51.4% were male, 48.6% were female, 11.6% were Hispanic or Latino, 83.9% were White, 3.4% were African American, 5.9% were Asian, 0.5% were American Indian or Alaska Native, <0.1% were Native Hawaiian or Pacific Islander, 1.0% were other races, and 4.5% were multiracial.<sup>6</sup> Demographic characteristics were similar among participants who received Moderna COVID-19 Vaccine and those who received placebo.

In a clinical study, the most frequent adverse reactions in participants 12 through 17 years of age were pain at the injection site (97.2%), headache (78.4%), fatigue (75.2%), myalgia (54.3%), chills (49.1%), arthralgia (34.6%), axillary swelling/tenderness (34.6%), nausea/vomiting (29.3%), swelling at the injection site (27.7%), erythema at the injection site (25.8%), and fever (13.7%).<sup>7</sup>

#### *Children 6 through 11 years of age*

Safety data for Moderna COVID-19 Vaccine in children were collected in an ongoing Phase 2/3 two-part randomised, observer-blind clinical trial conducted in the United States and Canada (NCT04796896).<sup>8</sup> Part 1 is an open-label phase of the trial for safety, dose selection, and immunogenicity and included 380 participants 6 through 11 years of age who received at least 1 dose (0.25 mL) of Moderna COVID-19 Vaccine.<sup>9</sup> Part 2 is the placebo-controlled phase for safety and included 4,002 participants 6 through 11 years of age who received at least one dose (0.25 mL) of Moderna COVID-19 Vaccine (n=3,007) or placebo (n=995).<sup>10</sup> No participants in Part 1 participated in Part 2.<sup>11</sup> Demographic characteristics were similar among participants who received Moderna COVID-19 Vaccine and those who received placebo.<sup>12</sup>

The most frequent adverse reactions in children 6 through 11 years of age following administration of the primary series were injection site pain (98.4%), fatigue (73%), headache (62%), myalgia (35.2%), chills (34.6%), nausea/vomiting (29.2%), axillary swelling/tenderness (26.9%), fever (25.9%), injection site erythema (24.3%), injection site swelling (22.5%), and arthralgia (21.2%).<sup>13</sup>

#### Tabulated list of adverse reactions from clinical studies and post-authorisation experience in individuals 6 years of age and older

The safety profile presented below is based on data generated in a placebo-controlled clinical study on 30,346 adults  $\geq 18$  years of age, another placebo-controlled clinical study with

3,726 participants 12 through 17 years of age, another clinical study with 4,002 participants 6 through 11 years of age, and post-marketing experience.

Adverse reactions reported are listed according to the following frequency convention:

Very common ( $\geq 1/10$ )

Common ( $\geq 1/100$  to  $< 1/10$ )

Uncommon ( $\geq 1/1,000$  to  $< 1/100$ )

Rare ( $\geq 1/10,000$  to  $< 1/1,000$ )

Very rare ( $< 1/10,000$ )

Not known (cannot be estimated from the available data)

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness (Table 1).

**Table 1: Adverse reactions from Moderna COVID-19 Vaccine clinical trials and post authorisation experience in individuals 6 years of age and older**

| <b>MedDRA system organ class</b>                            | <b>Frequency</b> | <b>Adverse reaction(s)</b>                                                                                |
|-------------------------------------------------------------|------------------|-----------------------------------------------------------------------------------------------------------|
| <b>Blood and lymphatic system disorders</b>                 | Very common      | Lymphadenopathy*                                                                                          |
| <b>Immune system disorders</b>                              | Not known        | Anaphylaxis<br>Hypersensitivity                                                                           |
| <b>Nervous system disorders</b>                             | Very common      | Headache                                                                                                  |
|                                                             | Uncommon         | Dizziness                                                                                                 |
|                                                             | Rare             | Acute peripheral facial paralysis**<br>Hypoaesthesia/<br>paraesthesia <sup>14</sup>                       |
| <b>Cardiac disorders</b>                                    | Very rare        | Myocarditis<br>Pericarditis                                                                               |
| <b>Gastrointestinal disorders</b>                           | Very common      | Nausea/vomiting                                                                                           |
| <b>Skin and subcutaneous tissue disorders</b>               | Common           | Rash                                                                                                      |
| <b>Musculoskeletal and connective tissue disorders</b>      | Very common      | Myalgia<br>Arthralgia                                                                                     |
| <b>General disorders and administration site conditions</b> | Very common      | Injection site pain<br>Fatigue<br>Chills<br>Pyrexia<br>Injection site swelling<br>Injection site erythema |
|                                                             | Common           | Injection site urticaria<br>Injection site rash<br>Delayed injection site                                 |

|  |          |                         |
|--|----------|-------------------------|
|  |          | reaction                |
|  | Uncommon | Injection site pruritus |
|  | Rare     | Facial swelling***      |

\*Lymphadenopathy was captured as axillary lymphadenopathy on the same side as the injection site. Other lymph nodes (e.g., cervical, supraclavicular) were affected in some cases.

\*\*Throughout the safety follow-up period, acute peripheral facial paralysis (or palsy) was reported by three participants in the vaccine group and one participant in the placebo group. Onset in the vaccine group participants was 22 days, 28 days, and 32 days after Dose 2.

\*\*\*There were two serious adverse events of facial swelling in vaccine recipients with a history of injection of dermatological fillers. The onset of swelling was reported 1 and 2 days, respectively, after vaccination.

### *Booster dose participants*

Study 3 is an ongoing Phase 2, randomised, observer-blind, placebo-controlled, dose-confirmation study to evaluate the safety, reactogenicity, and immunogenicity of the Moderna COVID-19 Vaccine in participants 18 years of age and older (NCT04405076).<sup>15</sup> In this study, 198 participants received two doses (0.5 mL 1 month apart) of the Moderna COVID-19 Vaccine primary series.<sup>16</sup> In an open-label phase of this study, 167 of those participants received a single booster dose (0.25 mL) at least 6 months after receiving the second dose of the primary series.<sup>17</sup> The solicited adverse reaction profile for the booster dose was similar to that after the second dose in the primary series.<sup>18</sup>

### *Booster dose following primary vaccination with another authorised or approved COVID-19 vaccine*

The safety of a Moderna COVID-19 Vaccine (0.25 mL) booster dose in individuals who completed primary vaccination with another authorised or approved COVID-19 Vaccine (heterologous booster dose) is inferred from the safety of a Moderna COVID-19 Vaccine (0.25 mL) booster dose administered following completion of a Moderna COVID-19 Vaccine primary series (homologous booster dose) and from data from an independent Phase 1/2 open-label clinical trial (NCT04889209) conducted in the United States that evaluated a heterologous booster dose (0.5 mL) of the Moderna COVID-19 Vaccine. In this study, adults who had completed primary vaccination with a Moderna COVID-19 Vaccine 2-dose series (N=151), a Janssen COVID-19 Vaccine single dose (N=156), or a Pfizer-BioNTech COVID-19 Vaccine 2-dose series (N=151) at least 12 weeks prior to enrolment and who reported no history of SARS-CoV-2 infection were randomised 1:1:1 to receive a booster dose of one of three vaccines: Moderna COVID-19 Vaccine (0.5 mL), Janssen COVID-19 Vaccine, or Pfizer-BioNTech COVID-19 Vaccine. Adverse events were assessed through 28 days after the booster dose. An overall review of adverse reactions reported following the Moderna COVID-19 Vaccine heterologous booster dose (0.5 mL) did not identify any new safety concerns, as compared with adverse reactions reported following Moderna COVID-19 Vaccine primary series doses or homologous booster dose (0.25 mL).

### **Post-authorisation experience**

Anaphylaxis, myocarditis, and pericarditis have been reported following Moderna COVID-19 Vaccine administration (see section 4.4).

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Vaccine, COVID-19 Vaccine, ATC code: J07BX03

#### Mechanism of action

Moderna COVID-19 Vaccine encodes for the pre-fusion stabilised Spike protein of SARS-CoV-2. After intramuscular injection, cells take up the lipid nanoparticle, effectively delivering the mRNA sequence into cells for translation into protein. The mRNA delivery system is based on the principle and observation that cells in vivo can take up mRNA, translate it, and express protein antigen(s) in the desired conformation. The delivered mRNA does not enter the cellular nucleus or interact with the genome, is nonreplicating, and is expressed transiently. The protein undergoes post-translational modification and trafficking resulting in properly folded, fully functional Spike protein that is inserted into the cellular membrane of the expressing cell(s). The Spike protein is membrane bound, mimicking the presentation of natural infection.

The expressed Spike protein of SARS-CoV-2 is then recognised by immune cells as a foreign antigen which elicits both T-cell and B-cell responses. The immune response to the Spike protein results in functional antibody and T-cell responses and in the generation of memory immune cell populations.

### **5.2 Clinical studies**

#### **Efficacy in adults 18 years of age and older**

Study 1 was randomised, placebo-controlled, observer-blind clinical study conducted in participants 18 years of age and older who were at increased risk of COVID-19 disease (NCT04470427). In addition, pre-specified cohorts of participants who were either  $\geq 65$  years of age or 18 to  $< 65$  years of age with comorbid medical conditions were included. A total of 30,351 participants<sup>19</sup> were followed for a median of 92 days (range: 1-122) for the development of COVID-19 disease.

The primary efficacy analysis population (referred to as the Per Protocol Set or PPS), included 28,207 participants who received a 2-dose regimen (at 0 and 1 month) of either Moderna COVID-19 Vaccine (n=14,134) or placebo (n=14,073), had a negative baseline SARS-CoV-2 status, and did not develop confirmed COVID-19 within 14 days after the second dose (Table 2). The PPS study population included 47.4% female, 52.6% male, 79.5% White, 19.7% Hispanic or Latino, and 9.7% African American, 4.6% Asian, and 6.2% other. The median age of participants was 53 years (range 18-95). Of the study participants, 22.6% were at increased risk of severe COVID-19 due to at least one pre-existing medical condition (chronic lung disease, significant



cardiac disease, severe obesity, diabetes, liver disease, or HIV infection). A dosing window of –7 to +14 days for administration of the second dose (scheduled at day 29) was allowed for inclusion in the PPS.

COVID-19 cases were confirmed by polymerase chain reaction (PCR) and by a clinical adjudication committee.

**Table 2: Primary efficacy analysis: confirmed COVID-19<sup>#</sup> regardless of severity starting 14 days after the 2<sup>nd</sup> dose – per-protocol set<sup>20</sup>**

| Age group (years) | Moderna COVID-19 Vaccine |                  |                                                   | Placebo        |                  |                                                   | % Vaccine efficacy (95% CI)* |
|-------------------|--------------------------|------------------|---------------------------------------------------|----------------|------------------|---------------------------------------------------|------------------------------|
|                   | Participants N           | COVID-19 cases n | Incidence rate of COVID-19 per 1,000 person-years | Participants N | COVID-19 cases n | Incidence rate of COVID-19 per 1,000 person-years |                              |
| Overall (≥18)     | 14,134                   | 11               | 3.328                                             | 14,073         | 185              | 56.510                                            | 94.1 (89.3, 96.8)            |
| 18 to <65         | 10,551                   | 7                | 2.875                                             | 10,521         | 156              | 64.625                                            | 95.6 (90.6, 97.9)            |
| ≥65               | 3,583                    | 4                | 4.595                                             | 3,552          | 29               | 33.728                                            | 86.4 (61.4, 95.2)            |

<sup>#</sup> COVID-19: symptomatic COVID-19 requiring positive RT-PCR (reverse transcription-polymerase chain reaction) result and at least 2 systemic symptoms or 1 respiratory symptom. Cases starting 14 days after the 2<sup>nd</sup> dose.

\*VE and 95% CI from the stratified Cox proportional hazard model

#### Efficacy against severe COVID-19

Among all participants in the PPS, no cases of severe COVID-19 were reported in the vaccine group compared with 30 cases reported in the placebo group (incidence rate 9.138 per 1,000 persons/years). Vaccine efficacy against severe COVID-19 was 100% (Table 3).

**Table 3: Secondary efficacy analysis: confirmed severe COVID-19<sup>#</sup> cases starting 14 days after the 2<sup>nd</sup> dose – per-protocol set<sup>21</sup>**

| Endpoint                           | Moderna COVID-19 Vaccine |                  |                                                   | Placebo        |                  |                                                   | % Vaccine efficacy (95% CI)* |
|------------------------------------|--------------------------|------------------|---------------------------------------------------|----------------|------------------|---------------------------------------------------|------------------------------|
|                                    | Participants N           | COVID-19 cases n | Incidence rate of COVID-19 per 1,000 person-years | Participants N | COVID-19 cases n | Incidence rate of COVID-19 per 1,000 person-years |                              |
| Severe* cases 14 days after Dose 2 | 14,134                   | 0                | NA                                                | 14,073         | 30               | 9.138                                             | 100%                         |

<sup>#</sup>Severe COVID-19 cases are defined as a confirmed COVID-19 as per the Primary Efficacy Endpoint case definition, plus any of the following:

-Clinical signs indicative of severe systemic illness, Respiratory Rate ≥ 30 per minute, Heart Rate ≥ 125 beats per minute, SpO<sub>2</sub> ≤ 93% on room air at sea level or PaO<sub>2</sub>/FIO<sub>2</sub> < 300 mm Hg, OR

-Respiratory failure or Acute Respiratory Distress Syndrome (ARDS), (defined as needing high-flow oxygen, non-invasive or mechanical ventilation, or ECMO), evidence of shock (systolic blood pressure < 90 mmHg, diastolic BP < 60 mmHg or requiring vasopressors), OR  
 -Significant acute renal, hepatic or neurologic dysfunction, OR  
 -Admission to an intensive care unit or death.

\* VE and 95% CI from the stratified Cox proportional hazard model

### Additional efficacy analyses

Subgroup analyses of vaccine efficacy 14 days after Dose 2 can be found in Table 4.

**Table 4: Subgroup analyses of vaccine efficacy - COVID-19 14 days after Dose 2 per adjudication committee assessments (primary efficacy analysis set) – per-protocol set<sup>22</sup>**

| Subgroup                | Moderna COVID-19 Vaccine |                  |                                                   | Placebo        |                  |                                                   | % Vaccine efficacy (95% CI)** |
|-------------------------|--------------------------|------------------|---------------------------------------------------|----------------|------------------|---------------------------------------------------|-------------------------------|
|                         | Participants N           | COVID-19 cases n | Incidence rate of COVID-19 per 1,000 person-years | Participants N | COVID-19 cases n | Incidence rate of COVID-19 per 1,000 person-years |                               |
| Overall High risk*      | 3,206                    | 4                | 5.227                                             | 3,167          | 43               | 57.202                                            | 90.9 (74.7, 96.7)             |
| High risk 18 to <65     | 2,155                    | 2                | 3.947                                             | 2,118          | 35               | 70.716                                            | 94.4 (76.9, 98.7)             |
| Not High risk 18 to <65 | 8,396                    | 5                | 2.594                                             | 8,403          | 121              | 63.054                                            | 95.9 (90.0, 98.3)             |
| Females                 | 6,768                    | 7                | 4.364                                             | 6,611          | 98               | 62.870                                            | 93.1 (85.2, 96.8)             |
| Males                   | 7,366                    | 4                | 2.352                                             | 7,462          | 87               | 50.730                                            | 95.4 (87.4, 98.3)             |

\* Participants at increased risk of severe COVID-19 due to at least one pre-existing medical condition (chronic lung disease, significant cardiac disease, severe obesity, diabetes, liver disease or HIV infection), regardless of age

\*\* VE and 95% CI from the stratified Cox proportional hazard model

### **Immunogenicity in immunocompromised recipients**

From an independent report (*Hall VG, Ferreira VH, Ku T et al. Randomized Trial of a Third Dose of mRNA-1273 Vaccine in Transplant Recipients. N Engl J Med*), a separate randomised controlled study has been conducted in 120 participants who had undergone various solid organ transplant procedures (heart, kidney, kidney-pancreas, liver, lung, pancreas) a median of 3.57 years previously (range 1.99-6.75 years). A third dose (0.5 mL) of Moderna COVID-19 Vaccine was administered to 60 participants approximately 2 months after they had received a second dose; saline placebo was given to 60 individuals for comparison (NCT04885907). Significant increases in levels of SARS-CoV-2 antibodies occurred four weeks after the third

dose in 55.0% of participants in the Moderna COVID-19 Vaccine group (33 of 60) and 17.5% of participants in the placebo group (10 of 57).

### **Efficacy in adolescents 12 through 17 years of age**

Study 2 is an ongoing Phase 2/3 randomised, placebo-controlled, observer-blind, clinical trial to evaluate the safety, reactogenicity, and effectiveness of the Moderna COVID-19 Vaccine in adolescents ages 12 to 17 years in the United States (NCT04649151).<sup>23</sup> Participants with a known history of SARS-CoV-2 infection were excluded from the study. A total of 3,732<sup>1</sup> participants were randomised 2:1 to receive 2 doses of the Moderna COVID-19 Vaccine or saline placebo 1 month apart.<sup>24</sup> Participants will be followed for efficacy and safety until 1 year after the second dose.

An efficacy analysis was performed in 3,236 participants who received at least Dose 1 of either Moderna COVID-19 Vaccine (n=2,163) or placebo (n=1,073), and had a negative baseline SARS-CoV-2 status (referred to as the modified Intent-to-Treat Set).<sup>25</sup> In the mITT set, 48.5% were female, 11.2% were Hispanic or Latino; 83.9% were White, 2.8% were African American, 6.3% were Asian, and 0.9% other races.<sup>26</sup> Between participants who received Moderna COVID-19 Vaccine and those who received placebo, there were no notable differences in demographics or pre-existing medical conditions.

COVID-19 was defined as the presence of at least one symptom from a list of COVID-19 symptoms occurring at least 14 days after Dose 1 and a positive nasopharyngeal (NP) swab or saliva sample for SARS-CoV-2 by RT-PCR (reverse transcription-polymerase chain reaction). Listed symptoms were fever (temperature  $> 38^{\circ}\text{C} \geq 100.4^{\circ}\text{F}$ ), or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle aches, or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea, or vomiting or diarrhoea.

There were 2 COVID-19 cases in the Moderna COVID-19 Vaccine group and 13 cases in the placebo group, with a vaccine efficacy of 92.7% (95% confidence interval of 67.8% to 99.2%) (Table 5).<sup>27</sup>

**Table 5: Efficacy analysis: COVID-19\* in participants 12 to 17 years of age starting 14 days after Dose 1 – modified intent-to-treat set<sup>28</sup>**

| Moderna COVID-19 Vaccine |                    |                                                   | Placebo          |                    |                                                   | % Vaccine efficacy (95% CI) <sup>†</sup> |
|--------------------------|--------------------|---------------------------------------------------|------------------|--------------------|---------------------------------------------------|------------------------------------------|
| Participants (N)         | COVID-19 cases (n) | Incidence rate of COVID-19 per 1,000 person-years | Participants (N) | COVID-19 cases (n) | Incidence rate of COVID-19 per 1,000 person-years |                                          |
| 2,163                    | 2                  | 3.828                                             | 1,073            | 13                 | 52.473                                            | 92.7 (67.8, 99.2)                        |

\* COVID-19: Presence of at least one symptom from a list of COVID-19 symptoms occurring at least 14 days after Dose 1 and a positive NP swab or saliva sample for SARS-CoV-2 by RT-PCR.

<sup>1</sup> 3,726 participants were randomised and received the first injection, with 1,240 on placebo and 2,486 on the Moderna COVID-19 Vaccine.

† Vaccine efficacy defined as  $1 - \text{ratio of incidence rate (Moderna COVID-19 Vaccine vs. placebo)}$ . The 95% CI of the ratio is calculated using the exact method conditional upon the total number of cases, adjusting for person-years.

### **Immunogenicity in adolescents 12 through 17 years of age<sup>29</sup>**

In Study 2 (NCT04649151), an analysis was conducted of SARS-CoV-2 50% neutralising titers and seroresponse rates 28 days after Dose 2 in a subset of adolescents aged 12 through 17 in Study 2 and in participants aged 18 through 25 in Study 1 who had no immunologic or virologic evidence of prior COVID-19 at baseline. Noninferior immune responses and seroresponse rates were demonstrated in a comparison of adolescents aged 12 through 17 years to participants aged 18 through 25 (Table 6).

**Table 6: Summary of geometric mean titer and seroresponse rate – comparison of adolescents aged 12 through 17 to participants aged 18 through 25 – per-protocol immunogenicity subset<sup>30</sup>**

| Assay                                                    | Time point                 | Moderna COVID-19 Vaccine       |                                | 12 through 17 years/<br>18 through 25 years          |                                              |
|----------------------------------------------------------|----------------------------|--------------------------------|--------------------------------|------------------------------------------------------|----------------------------------------------|
|                                                          |                            | 12 through 17 years<br>n=340   | 18 through 25 years<br>n=305   |                                                      |                                              |
|                                                          |                            | GLSM<br>(95% CI)*              | GLSM<br>(95% CI)*              | GMR<br>(95% CI)†                                     | Met<br>noninferiority<br>objective<br>(Y/N)‡ |
| SARS-CoV-2<br>neutralisation<br>assay – ID50<br>(titer)§ | 28 days<br>after<br>Dose 2 | 1401.7<br>(1276.3, 1539.4)     | 1301.3<br>(1177.0, 1438.8)     | 1.08<br>(0.94, 1.24)                                 | Y                                            |
|                                                          |                            | Seroresponse<br>%<br>(95% CI)¶ | Seroresponse<br>%<br>(95% CI)¶ | Difference in<br>seroresponse<br>rate %<br>(95% CI)# |                                              |
|                                                          |                            | 98.8<br>(97.0, 99.7)           | 98.6<br>(96.6, 99.6)           | 0.2<br>(-1.8, 2.4)                                   |                                              |

GLSM = Geometric least squares mean

GMR = Geometric mean ratio

n = Number of subjects with non-missing data at the corresponding timepoint

\* Antibody values reported as below the lower limit of quantification (LLOQ) are replaced by 0.5 x LLOQ. Values greater than the upper limit of quantification (ULOQ) are replaced by the ULOQ if actual values are not available.

† The log-transformed antibody levels are analysed using an analysis of covariance (ANCOVA) model with the group variable (adolescents in Study 2 and young adults in Study 1) as fixed effect. The resulted LS means, difference of LS means, and 95% CI are back transformed to the original scale for presentation.

‡ Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67 and the lower bound of the 2-sided 95% CI for difference in seroresponse rate is greater than -10%.

§ SARS-CoV-2 50% inhibitory dose (ID50) neutralisation titers were determined using a SARS-CoV-2 Spike-Pseudotyped Virus Neutralisation Assay. Quantification of SARS-CoV-2 neutralising antibodies utilises lentivirus particles expressing SARS-CoV-2 Spike protein on their surface and contains a firefly luciferase (Luc) reporter gene for quantitative measurements of infection by relative luminescence units (RLU). Neutralisation is measured as the serum dilution at which RLU is reduced by 50% (ID50) relative to mean RLU in virus control wells virus but after subtraction of mean RLU in cell control wells.

¶ Seroresponse due to vaccination specific to pseudovirus neutralising antibody ID50 titer at a subject level is defined as a change from below LLOQ to equal or above LLOQ, or at least a 3.3-fold rise if baseline is equal to or above LLOQ.

# Difference in seroresponse rate 95% CI is calculated using the Miettinen-Nurminen (score) confidence limits.

### Efficacy in children 6 through 11 years of age

The paediatric study is an ongoing Phase 2/3 randomised, placebo-controlled, observer-blind, clinical trial to evaluate the safety, reactogenicity, and effectiveness of the Moderna COVID-19 Vaccine in children ages 6 through 11 years in the United States and Canada (NCT04796896). Participants with a known history of SARS-CoV-2 infection were excluded from the study. A total of 4,011 participants were randomised 3:1 to receive 2 doses of the Moderna COVID-19 Vaccine or saline placebo 1 month apart. Participants will be followed for effectiveness and safety until 1 year after the second dose.<sup>31</sup>

A descriptive efficacy analysis evaluating confirmed COVID-19 cases accrued up to the data cutoff date of October 6, 2021 was performed in 3,556 participants who received two doses (0.25 mL at 0 and 1 month) of either the Moderna COVID-19 Vaccine (n=2,678) or placebo (n=878), and had a negative baseline SARS-CoV-2 status (referred to as the modified Intent-to-

Treat Set [mITT]). Between participants who received the Moderna COVID-19 Vaccine and those who received placebo, there were no notable differences in demographics.<sup>32</sup>

The median length of follow-up for efficacy for participants in the study was 50 days post Dose 1.

The efficacy information in children 6 through 11 years of age is presented in Table 7.

**Table 7: Efficacy analysis: COVID-19 and SARS-CoV-2 infections in participants 6 through 11 years of age starting 14 days after dose 1 – modified intent-to-treat set**

|                                                                      | Moderna COVID-19 Vaccine<br>N=2,672 |                                                            | Placebo<br>N=877 |                                                            | % Vaccine<br>Efficacy<br>(95% CI)* |
|----------------------------------------------------------------------|-------------------------------------|------------------------------------------------------------|------------------|------------------------------------------------------------|------------------------------------|
|                                                                      | Cases<br>(n)                        | Incidence Rate<br>of COVID-19<br>per 1,000<br>Person-Years | Cases<br>(n)     | Incidence Rate<br>of COVID-19<br>per 1,000<br>Person-Years |                                    |
| COVID-19 Cases -<br>Definition 1 <sup>a</sup>                        | 0                                   | 0                                                          | 13               | 152.027                                                    | 100.0<br>(89.3, NE)                |
| COVID-19 Cases -<br>Definition 2 <sup>b</sup>                        | 3                                   | 11.399                                                     | 14               | 163.810                                                    | 93.0<br>(75.1, 98.7)               |
| SARS-CoV-2<br>Infections<br>(regardless of<br>symptoms) <sup>c</sup> | 16                                  | 60.958                                                     | 26               | 306.853                                                    | 80.1<br>(61.5, 90.0)               |
| Asymptomatic<br>SARS-CoV-2<br>Infections <sup>d</sup>                | 13                                  | 49.529                                                     | 12               | 141.625                                                    | 65.0<br>(16.1, 85.3)               |

N = Number of participants at risk at 14 days after Dose 1 for specific efficacy endpoint.

NE = Not estimable

\* Vaccine efficacy defined as 1 — ratio of incidence rate (Moderna COVID-19 Vaccine vs. placebo). The 95% CI of the ratio is calculated using the exact method conditional upon the total number of cases, adjusting for person-years.

<sup>a</sup> Participant must have experienced at least two of the following systemic symptoms: fever ( $\geq 38^{\circ}\text{C}$  /  $\geq 100.4^{\circ}\text{F}$ ), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s); or the participant must have experienced at least one of the following respiratory signs/symptoms: cough, shortness of breath or difficulty breathing, or clinical or radiographical evidence of pneumonia; and the participant must have at least one NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by RT-PCR.

<sup>b</sup> Presence of at least one symptom from a list of COVID-19 symptoms and a positive NP swab or saliva sample for SARS-CoV-2 by RT-PCR. Listed symptoms were fever (temperature  $>38^{\circ}\text{C}$  /  $\geq 100.4^{\circ}\text{F}$ ), or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle aches, or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea, or vomiting or diarrhea.

<sup>c</sup> A combination of COVID-19 and asymptomatic SARS-CoV-2 infection for participants with negative SARS-CoV-2 status at baseline: binding antibody against SARS-CoV-2 nucleocapsid protein negative at Day 1 that becomes positive post-baseline, or positive RT-PCR test post-baseline.

<sup>d</sup> Absence of symptoms and infections as detected by RT-PCR or serology tests: absent of COVID-19 symptoms and at least 1 of the following: binding antibody level against SARS-CoV-2 nucleocapsid protein negative at Day 1 that becomes positive post-baseline, or positive RT-PCR test post-baseline at scheduled or unscheduled/illness visits.



### **Immunogenicity in children 6 through 11 years of age<sup>33</sup>**

An analysis evaluating SARS-CoV-2 50% neutralising titers and seroresponse rates 28 days after Dose 2 was conducted in subset of children aged 6 through 11 (n=134) in the paediatric study and in participants aged 18 through 25 (n=296) in the adult study (NCT04796896). Subjects had no immunologic or virologic evidence of prior SARS-CoV-2 infection at baseline. The GMR of the neutralising antibody titers in children 6 through 11 years of age compared to the 18- to 25-year-olds was 1.5 (95% CI: 1.3, 1.8). The difference in seroresponse rate was 0.6% (95% CI: -2.8, 2.8). Non-inferiority criteria (lower bound of the 95% CI for GMR > 0.67 and lower bound of the 95% CI of the seroresponse rate difference > -10%) were met.

### **Immunogenicity in booster dose participants**

Study 3 is an ongoing Phase 2, randomised, observer-blind, placebo-controlled, dose-confirmation study to evaluate the safety, reactogenicity, and immunogenicity of the Moderna COVID-19 Vaccine in participants 18 years of age and older (NCT04405076).<sup>34</sup> In this study, 198 participants received two doses (0.5 mL 1 month apart) of the Moderna COVID-19 Vaccine primary series.<sup>35</sup> In an open-label phase, 149 of those participants (Per-Protocol Set) received a single booster dose (0.25 mL) at least 6 months after receiving the second dose in the primary series.<sup>36</sup> A single booster dose (0.25 mL) was shown to be immunogenic at Day 29 post-booster dose and non-inferior to Day 57 immunogenicity of the primary series (two doses of 0.5 mL 1 month apart) in a subset of participants 18 years of age and older in Study 1.<sup>37</sup>

### **Immunogenicity of a booster dose following primary vaccination with another authorised or approved COVID-19 vaccine in adults 18 years of age and older**

Effectiveness of a Moderna COVID-19 Vaccine (0.25 mL) booster dose in individuals who completed primary vaccination with another authorised or approved COVID-19 Vaccine (heterologous booster dose) is inferred from immunogenicity data supporting effectiveness of a Moderna COVID-19 Vaccine (0.25 mL) booster dose administered following completion of a Moderna COVID-19 Vaccine primary series and from immunogenicity data from an independent Phase 1/2 open-label clinical trial (NCT04889209) conducted in the United States that evaluated a heterologous booster dose (0.5 mL) of the Moderna COVID-19 Vaccine. In this study, adults who had completed primary vaccination with a Moderna COVID-19 Vaccine 2-dose series (N=151), a Janssen COVID-19 Vaccine single dose (N=156), or a Pfizer-BioNTech COVID-19 Vaccine 2-dose series (N=151) at least 12 weeks prior to enrollment and who reported no history of SARS-CoV-2 infection were randomized 1:1:1 to receive a booster dose of one of three vaccines: Moderna COVID-19 Vaccine, Janssen COVID-19 Vaccine, or Pfizer-BioNTech COVID-19 Vaccine. Neutralizing antibody titers, as measured by a pseudovirus neutralization assay using a lentivirus expressing the SARS-CoV-2 Spike protein with D614G mutation, were assessed on Day 1 prior to administration of the booster dose and on Day 15 after the booster dose. A booster response to the Moderna COVID-19 Vaccine (0.5 mL) was demonstrated regardless of primary vaccination.

### **Immunogenicity in adult participants against the B.1.617.2 (Delta) variant<sup>38</sup>**

Serum samples were obtained from participants in Study 3 (Part B) pre-booster and on Day 29 post-booster. Results of the pseudovirion neutralisation assay (PsVNA) against the B.1.617.2 (Delta) variant showed that administration of the Moderna COVID-19 Vaccine booster (50 mcg) induced an 18-fold rise in neutralising titers against the Delta variant compared with pre-booster

levels (Geometric mean fold rise (GMFR) = 18.97; 95% CI, 16.72, 21.53; overall group, n = 295).

In the overall Study 3 (Part B) group (n = 293), the pre-booster neutralising antibodies (nAb) Geometric mean titre (GMT) for the Delta variant was 42.27 (95% CI: 37.19, 48.04; n = 293) and 28 days post-booster, the GMT was 803.51 (95% CI: 731.42, 882.70; n = 295). Over 90% of booster recipients in the overall group (92.2%; 95% CI: 88.5, 95.0%; n = 293) met the definition of a seroresponse for the Delta variant (using a 4-fold increase from pre-booster baseline).

Administration of the 50 µg mRNA-1273 prototype booster resulted in robust increases in nAb responses against the Delta variant regardless of the priming dose. Participants primed with 50 µg had a GMFR of 20.89 (95% CI: 17.54, 24.87); those primed with 100 µg had a GMFR of 17.28 (95% CI: 14.38, 20.77), showing the consistency in responses regardless of priming dose.

Additional analyses of Delta variant nAb GMT by age group have been conducted. nAb responses in older adults are numerically similar to those observed in the younger groups (749.94 vs. 822.98).

The GMFR (Day 29 post-booster: pre-booster) achieved by Moderna COVID-19 Vaccine booster, measured by the Delta pseudovirus assay (18.97; 95% CI: 16.72, 21.53), points to the ability of the prototype vaccine booster to enhance a breadth of nAb responses, including against the highly transmissible Delta variant. Just as the Moderna COVID-19 Vaccine booster generated enhanced nAb levels against the original strain (GMFR 15.06 [95% CI: 13.43, 16.89]), it also was able to broaden and increase nAb levels against Delta variant.

### **Immunogenicity in children against the B.1.617.2 (Delta) variant<sup>39</sup>**

Additional data on the immunogenicity of the Moderna COVID-19 Vaccine against the Delta variant comes from paediatric study. Serum samples were obtained at baseline and on Day 57 from participants 6 to <12 years of age.

In the per-protocol immunogenicity subset (n=134), the baseline nAb GMT against Delta (measured by PsVNA ID50) in children 6 years to < 12 years old was below the LLOQ; 28 days after 2 doses of 50 mcg of the Moderna COVID-19 Vaccine, serum nAb GMT was 756.46 (95% CI: 650.99, 878.77). Furthermore, 99.3% of children met the definition of seroresponse against the Delta variant. The GMFR from baseline to D57 was 81.77 (95% CI: 70.38, 95.00) for the Delta variant.

## **5.2 Pharmacokinetic properties**

Not applicable.

## **5.3 Carcinogenesis, mutagenesis, impairment of fertility**

Conventional studies of repeat dose toxicity and reproductive and developmental toxicity in animals and *in vitro* did not reveal any risks for humans.



### General toxicity

Intramuscular administration of mRNA to rats (up to 4 doses exceeding the human dose once every 2 weeks, resulting in higher doses in rats due to body weight differences) revealed some injection erythema and oedema and transient changes in haematology (neutrophils, eosinophils, lymphocytes, activated partial thromboplastin time, fibrinogen), chemistry (albumin and globulin), and increased cellularity and/or inflammation of lymphoid organs consistent with an inflammatory response, as well as vacuolation or hypertrophy in hepatocytes or Kupffer cells, without evidence of liver injury. All effects were reversible.

### Genotoxicity/carcinogenicity

In vitro and in vivo genotoxicity studies were conducted with the novel lipid components of the vaccine. Results suggest the genotoxicity potential to humans is low. Carcinogenicity studies were not performed.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Heptadecan-9-yl 8-((2-hydroxyethyl) (6-oxo-6-(undecyloxy) hexyl) amino)octanoate (Lipid SM-102)

Cholesterol

1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC)

1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000 (PEG2000-DMG)

Trometamol

Trometamol hydrochloride

Acetic acid

Sodium acetate trihydrate

Sucrose

Water for Injections

### **6.2 Incompatibilities**

This medicinal product must not be mixed with other medicinal products or diluted.

### **6.3 Shelf life**

9 months at -50°C to -15°C.

The unopened vaccine may be stored refrigerated at 2°C to 8°C, protected from light, for maximum 30 days.

Once thawed the vaccine should not be re-frozen.

The vial may be stored at 8°C to 25°C for a total of 24 hours after removal from refrigerated conditions.

Vials may be held for up to 12 hours at 2°C to 25°C after initial puncture.

#### **6.4 Special precautions for storage**

Moderna COVID-19 Vaccine multiple-dose vials are stored frozen between -50° to -15°C (-58° to 5°F).

Any freezer that reliably maintains an average temperature between -50° and -15°C (-58° to 5°F) and has a separate sealed freezer door is acceptable for storing Moderna COVID-19 Vaccine.

Moderna COVID-19 Vaccine can be stored refrigerated between 2° to 8°C (36° to 46°F) for up to 30 days if not entered (needle-punctured). Do not refreeze.

The total storage time of a vial after removal from refrigerated conditions should not exceed 24 hours at 8° to 25°C (46° to 77°F). Do not refreeze.

Once the vial has been entered (needle-punctured) to withdraw the initial dose, the product should be used immediately and be discarded after 12 hours. Do not refreeze.

Protect from light.

#### **Transportation of thawed vials in liquid state at 2° to 8°C (36° to 46°F)**

If transport at -50° to -15°C (-58° to 5°F) is not feasible, available data support transportation of one or more thawed vials in liquid state for up to 12 hours at 2° to 8°C (36° to 46°F) when shipped using shipping containers which have been qualified to maintain 2° to 8°C (36° to 46°F) and under routine road and air transport conditions with shaking and vibration minimised. Once thawed and transported in liquid state at 2° to 8°C (36° to 46°F), vials should not be refrozen and should be stored at 2° to 8°C (36° to 46°F) until use.

#### **6.5 Nature and contents of container**

5 mL dispersion in a vial (type 1 or type 1 equivalent glass) with a stopper (chlorobutyl rubber) and a flip-off plastic cap with seal (aluminum seal).

Each vial contains 5 mL.

Pack size: 10 multidose vials

#### **6.6 Special precautions for disposal and other handling**

Moderna COVID-19 Vaccine vials are for multiple use. Ten (10) doses of 0.5 mL volume each or a maximum of twenty (20) doses of 0.25 mL volume can be withdrawn from each multiple-dose vial.

Moderna COVID-19 Vaccine multiple-dose vials are stored frozen between -50°C to -15°C.

Moderna COVID-19 Vaccine can be stored refrigerated between 2° to 8°C (36° to 46°F) for up to 30 days if not entered (needle-punctured).

Thaw each vial before use:

- Thaw in refrigerated conditions between 2°C to 8°C for 2 hours and 30 minutes. Let each vial stand at room temperature for 15 minutes before administering.
- Alternatively, thaw at room temperature between 15°C to 25°C for 1 hour.
- Do not re-freeze vials after thawing.

Swirl the vial gently after thawing and between each withdrawal. Do not shake.

Moderna COVID-19 Vaccine is a white to off-white dispersion. It may contain white or translucent product-related particulates.

Inspect Moderna COVID-19 Vaccine vials visually for foreign particulate matter and/or discoloration prior to administration. If either of these conditions exists, the vaccine should not be administered.

Withdraw each dose of vaccine from the vial using a new sterile needle and syringe (preferentially a low dead-volume syringe and/or needle) for each injection to prevent transmission of infectious agents from one person to another. Pierce the stopper, preferably at a different site each time. Do not puncture the vial more than 20 times.<sup>40</sup> The dose in the syringe should be used promptly.

This product is preservative free. Once the vial has been entered (needle-punctured) to withdraw the initial dose, the product should be used immediately and be discarded after 12 hours. Do not refreeze.

Thawed vials and filled syringes can be handled in room light conditions.

Any unused vaccine or waste material should be disposed of in accordance with local requirements.

International birth date: December 18, 2020

## 10. DATE OF REVISION OF THE TEXT

| Date                           | Version | Summary of changes                                                                                                                                                                                                                                      |
|--------------------------------|---------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| November 28 <sup>th</sup> 2020 | 1.1     | QC corrections                                                                                                                                                                                                                                          |
| December 8 <sup>rd</sup> 2020  | 1.2     | Correction to Undesirable Effects summary text; correction/addition of footnotes to adverse reactions and efficacy tables; updates to shelf life, excipients, and container description<br>Correction of instructions for handling after first puncture |

|                                |     |                                                                                                                                                                                                                                                                                                                                          |
|--------------------------------|-----|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| December 16 <sup>th</sup> 2020 | 2.0 | Modified Pregnancy/lactation section to reflect availability of DART study<br>Updated phase 3 data with data from Nov 25 snapshot                                                                                                                                                                                                        |
| December 18 <sup>th</sup> 2020 | 2.1 | Minor updates to align with Company Core Safety Information and editorial corrections                                                                                                                                                                                                                                                    |
| December 29 <sup>th</sup> 2020 | 3.0 | Updates to align with CCSI V3.0 to include information on anaphylaxis and editorial corrections.<br>Additional n/c data added to support SmPC                                                                                                                                                                                            |
| February 1 <sup>st</sup> 2021  | 3.1 | Updates to include adverse reaction frequency table, minor updates to add/change text to support SmPC and US PI, technical updates to ingredient descriptions, addition of International Birth Date                                                                                                                                      |
| May 6 <sup>th</sup> 2021       | 4.0 | Addition of 30-minute observation recommendation for anaphylaxis in Warnings. Addition of delayed injection site reaction data to Undesirable Effects. Updates to and addition of storage and handling conditions; removal of grey shading as noted to sections 4.2, 4.6 and 4.7. Typographical edits as noted in the annotated version. |
| June 1 <sup>st</sup> 2021      | 5.0 | Addition of Adolescent EUA data (sections 4.8, and 5.2). Addition of brand name. Typographical edits as noted in the annotated version.                                                                                                                                                                                                  |
| June 25 2021                   | 6.0 | Addition of myocarditis and pericarditis Warnings (section 4.4) and post authorisation experience (section 4.8).                                                                                                                                                                                                                         |

|                  |      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|------------------|------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| August 13 2021   | 7.0  | Addition of immunocompromised booster data (sections 4.2, 4.4, 4.8, and 5.1).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| August 30 2021   | 8.0  | Addition of elasomeran INN (section 1); addition of booster data in sections 2, 4.2, 4.8 and 5.2. Clarifications to immunocompromised text in sections 4.4, 4.8 and 5.2. Edits to accommodate booster in sections 6.5 and 6.6.                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| November 3 2021  | 9.0  | Addition of paediatric data (6-11 yr olds) and related edits in sections 4.1, 4.2, 4.8 and 5.2. Addition of heterologous boosting data in sections 4.2, 4.8 and 5.2.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| November 17 2021 | 10.0 | Extension in shelf life to 9 months and deletion of dry ice statements.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| December 10 2021 | 11.0 | <p><b>Section 4.4:</b> Myocarditis/pericarditis: redline edits were discussed and agreed upon at SRB on 10 Dec 2021.</p> <p><b>Section 4.6:</b> Breastfeeding: aligned text with US Fact Sheets.</p> <p><b>Section 4.8:</b> removed US-based ADR content and re-organized and simplified to establish Table 1 as the most current and cumulative reflection of ADRs. Minor updates to align with the IB.</p> <p><b>Table 1:</b> addition of paraesthesia per PBRER outcome. Myocarditis and pericarditis frequency reclassified from Not Known to Very Rare to reflect latest available data.</p> <p><b>Section 5.2:</b> Addition of Adults and Peds Delta data.</p> |

## REFERENCES

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- <sup>1</sup> Module 2.5.2.2
- <sup>2</sup> Module 2.5.7.5
- <sup>3</sup> Module 2.5, section 2.5.1.4.1 Study mRNA-1273-P201
- <sup>4</sup> PPD\_Re-QC\_IND 19745\_Shell Templates\_CB ER\_DSS 2\_15Dec2020\_Version1-1\_For Sponsor Review and Incorporation\_16Dec2020\_safety tables.doc Table 9 (sum of vaccine + placebo P301)
- <sup>5</sup> Table 1.4 Summary of Study Duration by Age Group Safety Set (Number of Subjects, n (%) Received First Injection)
- <sup>6</sup> Module 2.5, Table 3 Subject Demographics and Baseline Characteristics by Age Group Safety Set (Overall)
- <sup>7</sup> Table 3.1.1.3 Summary of Subjects with Solicited Adverse Reactions Within 7 Days After Any Injection by Age Group and Grade Solicited Safety Set (N1)
- <sup>8</sup> 2.5.2.5 Overview of Clinical Development of mRNA-1273 for Children 6 Months to < 12 Years of Age; Module 2.5.5.1.3
- <sup>9</sup> Table 14.1.3.1.1 Subject Demographics and Baseline Characteristics by Age Group and Dose Level in Part 1 Safety Set
- <sup>10</sup> 2.5.2.5 Overview of Clinical Development of mRNA-1273 for Children 6 Months to < 12 Years of Age; Table 14.1.3.2 Subject Demographics and Baseline Characteristics by Age Group Safety Set
- <sup>11</sup> 2.5.2.5 Overview of Clinical Development of mRNA-1273 for Children 6 Months to < 12 Years of Age
- <sup>12</sup> 2.5.5.1.2 Demographics and Baseline Characteristics
- <sup>13</sup> Table 14.3.1.1.3.2.1 Summary of Subjects with Solicited Adverse Reactions Within 7 Days After Any Injection by Age Group and Grade Solicited Safety Set
- <sup>14</sup> Based on the analysis of available safety data presented as of 30 June 2021 in PBRER #1. P301: 14 cases in the mRNA-1273 arm [n=15,184] = 0.0922%
- <sup>15</sup> Module 2.5, section 2.5.1.4.1 Study mRNA-1273-P201
- <sup>16</sup> IND 19745 SN0176 Executive Summary P201 Part B (100 mcg Prime Part A D57)
- <sup>17</sup> Module 2.5, section 2.5.4.1.1.2 Disposition and section 2.5.4.1.1 Analysis Sets (Solicited Safety Set)
- <sup>18</sup> Module 2.5, section 2.5.5 Overview of Safety
- <sup>19</sup> PPD\_Re-QC\_IND 19745\_Shell Templates\_CB ER\_DSS 2\_15Dec2020\_Version1-1\_For Sponsor Review and Incorporation\_16Dec2020\_safety tables.doc Table 3
- <sup>20</sup> PPD\_Re-QC\_IND 19745\_Shell Templates\_CB ER\_DSS 2\_15Dec2020\_Version1-1\_For Sponsor Review and Incorporation\_16Dec2020\_safety tables.doc Table 4
- <sup>21</sup> PPD\_Re-QC\_IND 19745\_Shell Templates\_CB ER\_DSS 2\_15Dec2020\_Version1-1\_For Sponsor Review and Incorporation\_16Dec2020\_safety tables.doc Table 6
- <sup>22</sup> PPD\_Re-QC\_IND 19745\_Shell Templates\_CB ER\_DSS 2\_15Dec2020\_Version1-1\_For Sponsor Review and Incorporation\_16Dec2020\_safety tables.doc Table 7
- <sup>23</sup> Emergency Use Authorisation (EUA) Request, Section 6.2.1.1.1 Disposition
- <sup>24</sup> Emergency Use Authorisation (EUA) Request, Section 6.2.1.1.1 Disposition
- <sup>25</sup> Table 2.8.2.1 Analysis of Incidence Rate of Secondary Definition of COVID-19 Starting 14 Days After First Injection mITT1 Set
- <sup>26</sup> Table 1.3.3, Subject Demographics and Baseline Characteristics by Age Group mITT1 Set
- <sup>27</sup> Table 2.8.2.1 Analysis of Incidence Rate of Secondary Definition of COVID-19 Starting 14 Days After First Injection mITT1 Set
- <sup>28</sup> Table 2.8.2.1 Analysis of Incidence Rate of Secondary Definition of COVID-19 Starting 14 Days After First Injection mITT1 Set
- <sup>29</sup> Table 2.1.1.3.1 Analysis of Pseudovirus Neutralizing Antibody ID50 and ID80 Titers -ANCOVA Model Per-Protocol Immunogenicity Subset
- <sup>30</sup> Table 2.1.2.3.1 Analysis of Pseudovirus Neutralizing Antibody ID50 and ID80 Titers — Seroreponse Rate Per-Protocol Immunogenicity Subset
- <sup>31</sup> Module 2.5.2.5, 2.5.5.2.2.3.1; Table 14.1.1.1.2
- <sup>32</sup> Module 2.5.5.1.1, 2.5.5.1.2, 2.5.5.2.2.3.3; Table 14.1.2.1.2
- <sup>33</sup> 2.5.5.2.1 Statistical Methods Used for P204; 2.5.5.2.2.2 Immunogenicity; Table 14.2.1.1.3.4.1 Analysis of Pseudovirus Neutralizing Antibody ID50 and ID80 Titers by Age Group and Dose Level in Part 1 Expansion Per-

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Protocol Immunogenicity Subset; Table 14.2.1.2.3.4.1 Analysis of Pseudovirus Neutralizing Antibody ID50 and ID80 Titers by Age Group and Dose Level in Part 1 Expansion —Seroresponse Rate Per-Protocol Immunogenicity Subset

<sup>34</sup> Module 2.5, section 2.5.1.4.1 Study mRNA-1273-P201

<sup>35</sup> Module 2.5, section 2.5.1.4.1 Study mRNA-1273-P201

<sup>36</sup> Module 2.5, section 2.5.1.4.1 Study mRNA-1273-P201 and section 2.5.4.1.1 Analysis Sets (Per-Protocol Set)

<sup>37</sup> Module 2.5, section 2.5.4.2.2 Results

<sup>38</sup> Module 2.5, section 2.5.5.2.2.1.1

<sup>39</sup> Module 2.5, section 2.5.1

<sup>40</sup> EUA 27073 SN0083 3.2.P.2.4 Attachment PD-MEM-0517 USP<381> up to 20 punctures

**20.2. Appendix 2 Cumulative Summary Tabulations of Serious Adverse Events  
from Clinical Trials**



**Cumulative Summary Tabulations of SAEs from CTs (Through 31 December 2021)**

| Event Counts                                |                         |            |               |                 |               |           |             |
|---------------------------------------------|-------------------------|------------|---------------|-----------------|---------------|-----------|-------------|
| SOC - PT                                    | mRNA-1273 vs<br>Placebo | mRNA-1273  | mRNA-1273.211 | mRNA-1273.617.2 | mRNA-1273.213 | Placebo   | Grand Total |
| <b>Blood and lymphatic system disorders</b> | <b>5</b>                | <b>29</b>  | <b>1</b>      |                 |               | <b>5</b>  | <b>40</b>   |
| Anaemia                                     | 1                       | 14         | 1             |                 |               | 2         | 18          |
| Anaemia macrocytic                          |                         |            |               |                 |               | 1         | 1           |
| Blood loss anaemia                          |                         | 3          |               |                 |               | 1         | 4           |
| Febrile neutropenia                         | 1                       | 3          |               |                 |               |           | 4           |
| Immune thrombocytopenia                     |                         | 1          |               |                 |               |           | 1           |
| Iron deficiency anaemia                     | 1                       | 2          |               |                 |               |           | 3           |
| Leukocytosis                                |                         | 3          |               |                 |               |           | 3           |
| Lymphadenopathy                             |                         | 1          |               |                 |               |           | 1           |
| Pancytopenia                                |                         | 1          |               |                 |               |           | 1           |
| Splenic infarction                          |                         | 1          |               |                 |               |           | 1           |
| Thrombocytopenia                            | 2                       |            |               |                 |               |           | 2           |
| Thrombocytosis                              |                         |            |               |                 |               | 1         | 1           |
| <b>Cardiac disorders</b>                    | <b>38</b>               | <b>254</b> | <b>2</b>      | <b>1</b>        |               | <b>41</b> | <b>336</b>  |
| Acute coronary syndrome                     | 1                       | 4          |               |                 |               |           | 5           |
| Acute left ventricular failure              | 1                       | 7          |               |                 |               | 1         | 9           |
| Acute myocardial infarction                 | 1                       | 26         |               |                 |               | 6         | 33          |
| Angina pectoris                             | 1                       | 16         |               |                 |               | 2         | 19          |
| Angina unstable                             |                         | 7          |               |                 |               |           | 7           |
| Aortic valve incompetence                   |                         | 3          |               |                 |               |           | 3           |
| Aortic valve prolapse                       |                         | 1          |               |                 |               |           | 1           |
| Aortic valve stenosis                       |                         | 4          |               |                 |               |           | 4           |
| Arrhythmia                                  |                         | 2          |               |                 |               | 1         | 3           |
| Arteriosclerosis coronary artery            |                         | 1          |               |                 |               |           | 1           |
| Arteriospasm coronary                       |                         | 1          |               |                 |               |           | 1           |
| Atrial fibrillation                         | 5                       | 29         |               | 1               |               | 8         | 43          |
| Atrial flutter                              | 1                       | 10         |               |                 |               | 1         | 12          |
| Atrial tachycardia                          |                         | 2          |               |                 |               |           | 2           |
| Atrioventricular block complete             |                         | 4          |               |                 |               | 1         | 5           |
| Atrioventricular block second degree        |                         |            |               |                 |               | 1         | 1           |
| Bradycardia                                 | 2                       | 7          | 1             |                 |               |           | 10          |
| Cardiac arrest                              | 1                       | 6          |               |                 |               |           | 7           |
| Cardiac failure                             | 2                       | 4          |               |                 |               | 1         | 7           |
| Cardiac failure acute                       | 1                       | 5          |               |                 |               |           | 6           |
| Cardiac failure chronic                     |                         | 1          |               |                 |               |           | 1           |
| Cardiac failure congestive                  | 3                       | 24         |               |                 |               | 5         | 32          |
| Cardiac flutter                             |                         | 1          |               |                 |               |           | 1           |
| Cardiomyopathy                              |                         | 3          |               |                 |               |           | 3           |
| Cardio-respiratory arrest                   | 3                       | 1          |               |                 |               |           | 4           |
| Coronary artery disease                     | 3                       | 26         |               |                 |               | 3         | 32          |
| Coronary artery insufficiency               |                         | 1          |               |                 |               |           | 1           |
| Coronary artery occlusion                   |                         | 5          |               |                 |               |           | 5           |
| Coronary artery stenosis                    |                         | 1          |               |                 |               |           | 1           |
| Ischaemic cardiomyopathy                    |                         | 1          |               |                 |               |           | 1           |
| Left ventricular failure                    |                         | 2          |               |                 |               |           | 2           |
| Microvascular coronary artery disease       |                         | 1          |               |                 |               |           | 1           |
| Mitral valve incompetence                   |                         | 4          |               |                 |               |           | 4           |

| Event Counts                                      |                         |            |               |                 |               |           |             |
|---------------------------------------------------|-------------------------|------------|---------------|-----------------|---------------|-----------|-------------|
| SOC - PT                                          | mRNA-1273 vs<br>Placebo | mRNA-1273  | mRNA-1273.211 | mRNA-1273.617.2 | mRNA-1273.213 | Placebo   | Grand Total |
| Myocardial infarction                             | 11                      | 21         | 1             |                 |               | 4         | 37          |
| Myocardial ischaemia                              |                         | 1          |               |                 |               |           | 1           |
| Myocarditis                                       |                         | 1          |               |                 |               |           | 1           |
| Palpitations                                      |                         | 1          |               |                 |               |           | 1           |
| Paroxysmal atrioventricular block                 |                         | 1          |               |                 |               |           | 1           |
| Pericardial effusion                              |                         | 2          |               |                 |               |           | 2           |
| Pericarditis                                      | 2                       | 3          |               |                 |               | 4         | 9           |
| Pulseless electrical activity                     |                         | 1          |               |                 |               |           | 1           |
| Sinus node dysfunction                            |                         | 1          |               |                 |               |           | 1           |
| Sinus tachycardia                                 |                         |            |               |                 |               | 2         | 2           |
| Stress cardiomyopathy                             |                         | 3          |               |                 |               |           | 3           |
| Supraventricular tachycardia                      |                         | 4          |               |                 |               |           | 4           |
| Tachycardia                                       |                         | 1          |               |                 |               |           | 1           |
| Ventricular arrhythmia                            |                         |            |               |                 |               | 1         | 1           |
| Ventricular tachycardia                           |                         | 4          |               |                 |               |           | 4           |
| <b>Congenital, familial and genetic disorders</b> | <b>1</b>                | <b>2</b>   |               |                 |               | <b>1</b>  | <b>4</b>    |
| Arnold-Chiari malformation                        |                         | 2          |               |                 |               |           | 2           |
| Pectus excavatum                                  | 1                       |            |               |                 |               |           | 1           |
| Talipes                                           |                         |            |               |                 |               | 1         | 1           |
| <b>Ear and labyrinth disorders</b>                |                         | <b>6</b>   |               | <b>1</b>        |               |           | <b>7</b>    |
| Vertigo                                           |                         | 5          |               | 1               |               |           | 6           |
| Vertigo positional                                |                         | 1          |               |                 |               |           | 1           |
| <b>Endocrine disorders</b>                        |                         | <b>7</b>   |               |                 |               |           | <b>7</b>    |
| Adrenal mass                                      |                         | 1          |               |                 |               |           | 1           |
| Autoimmune thyroiditis                            |                         | 1          |               |                 |               |           | 1           |
| Basedow's disease                                 |                         | 1          |               |                 |               |           | 1           |
| Goitre                                            |                         | 1          |               |                 |               |           | 1           |
| Hyperthyroidism                                   |                         | 2          |               |                 |               |           | 2           |
| Inappropriate antidiuretic hormone secretion      |                         | 1          |               |                 |               |           | 1           |
| <b>Eye disorders</b>                              | <b>2</b>                | <b>8</b>   |               |                 |               |           | <b>10</b>   |
| Diplopia                                          |                         | 2          |               |                 |               |           | 2           |
| Optic disc drusen                                 |                         | 1          |               |                 |               |           | 1           |
| Retinal artery occlusion                          |                         | 2          |               |                 |               |           | 2           |
| Retinal detachment                                | 1                       | 2          |               |                 |               |           | 3           |
| Retinal tear                                      | 1                       | 1          |               |                 |               |           | 2           |
| <b>Gastrointestinal disorders</b>                 | <b>29</b>               | <b>159</b> | <b>2</b>      |                 |               | <b>16</b> | <b>206</b>  |
| Abdominal discomfort                              |                         | 1          |               |                 |               |           | 1           |
| Abdominal hernia                                  |                         | 2          |               |                 |               | 1         | 3           |
| Abdominal mass                                    |                         | 1          |               |                 |               |           | 1           |
| Abdominal pain                                    | 3                       | 8          |               |                 |               |           | 11          |
| Abdominal pain lower                              |                         |            |               |                 |               | 1         | 1           |
| Abdominal pain upper                              | 2                       | 2          |               |                 |               |           | 4           |
| Abdominal rigidity                                |                         | 1          |               |                 |               |           | 1           |
| Chronic gastritis                                 |                         | 1          |               |                 |               |           | 1           |
| Colitis                                           | 2                       | 3          |               |                 |               | 3         | 8           |
| Colitis ischaemic                                 |                         | 2          |               |                 |               |           | 2           |
| Constipation                                      |                         | 2          |               |                 |               |           | 2           |
| Crohn's disease                                   |                         | 1          |               |                 |               |           | 1           |
| Dental caries                                     |                         | 1          |               |                 |               |           | 1           |

| Event Counts                       |                         |           |               |                 |               |         |             |
|------------------------------------|-------------------------|-----------|---------------|-----------------|---------------|---------|-------------|
| SOC - PT                           | mRNA-1273 vs<br>Placebo | mRNA-1273 | mRNA-1273.211 | mRNA-1273.617.2 | mRNA-1273.213 | Placebo | Grand Total |
| Diarrhoea                          | 3                       | 3         |               |                 |               |         | 6           |
| Diverticular perforation           |                         | 1         |               |                 |               |         | 1           |
| Diverticulum                       |                         | 1         |               |                 |               |         | 1           |
| Duodenal ulcer                     |                         | 2         |               |                 |               |         | 2           |
| Duodenal ulcer haemorrhage         | 1                       | 1         |               |                 |               |         | 2           |
| Duodenal ulcer perforation         | 1                       | 2         |               |                 |               |         | 3           |
| Dysphagia                          |                         | 4         |               |                 |               |         | 4           |
| Enteritis                          |                         | 2         |               |                 |               |         | 2           |
| Enterocolitis                      |                         | 1         |               |                 |               |         | 1           |
| Enterovesical fistula              |                         | 2         |               |                 |               |         | 2           |
| Gastric perforation                | 1                       |           |               |                 |               |         | 1           |
| Gastric ulcer                      |                         | 2         |               |                 |               |         | 2           |
| Gastric ulcer haemorrhage          | 1                       |           |               |                 |               |         | 1           |
| Gastritis                          |                         |           |               |                 |               | 2       | 2           |
| Gastrointestinal haemorrhage       | 1                       | 10        |               |                 |               | 2       | 13          |
| Gastrointestinal motility disorder |                         | 1         |               |                 |               |         | 1           |
| Gastrooesophageal reflux disease   | 1                       | 6         |               |                 |               |         | 7           |
| Haematemesis                       |                         | 1         |               |                 |               | 1       | 2           |
| Haematochezia                      |                         | 1         | 1             |                 |               |         | 2           |
| Haemoperitoneum                    |                         | 1         |               |                 |               |         | 1           |
| Hiatus hernia                      | 1                       | 3         |               |                 |               | 1       | 5           |
| Ileal perforation                  |                         | 1         |               |                 |               |         | 1           |
| Ileus                              |                         | 6         |               |                 |               |         | 6           |
| Impaired gastric emptying          |                         | 2         |               |                 |               |         | 2           |
| Inguinal hernia                    | 1                       |           |               |                 |               |         | 1           |
| Internal hernia                    |                         | 1         |               |                 |               |         | 1           |
| Intestinal haemorrhage             |                         | 1         |               |                 |               |         | 1           |
| Intestinal ischaemia               |                         | 1         |               |                 |               |         | 1           |
| Intestinal obstruction             |                         | 11        |               |                 |               |         | 11          |
| Intestinal perforation             |                         | 2         |               |                 |               |         | 2           |
| Intestinal pseudo-obstruction      |                         | 1         |               |                 |               |         | 1           |
| Intra-abdominal fluid collection   | 1                       |           |               |                 |               |         | 1           |
| Intussusception                    |                         | 1         |               |                 |               |         | 1           |
| Large intestinal haemorrhage       |                         | 1         |               |                 |               |         | 1           |
| Large intestinal obstruction       |                         | 2         |               |                 |               |         | 2           |
| Large intestine perforation        |                         | 4         |               |                 |               |         | 4           |
| Lower gastrointestinal haemorrhage |                         | 1         |               |                 |               |         | 1           |
| Lumbar hernia                      |                         | 1         |               |                 |               |         | 1           |
| Nausea                             | 1                       | 5         |               |                 |               | 1       | 7           |
| Obstructive pancreatitis           |                         | 1         |               |                 |               |         | 1           |
| Oesophageal rupture                |                         | 2         |               |                 |               |         | 2           |
| Oesophageal spasm                  | 1                       |           |               |                 |               |         | 1           |
| Oesophagitis                       |                         | 1         |               |                 |               |         | 1           |
| Pancreatic mass                    |                         | 1         |               |                 |               |         | 1           |
| Pancreatitis                       | 1                       | 8         | 1             |                 |               | 2       | 12          |
| Pancreatitis acute                 | 1                       | 6         |               |                 |               |         | 7           |
| Pancreatitis haemorrhagic          |                         | 1         |               |                 |               |         | 1           |
| Pancreatitis relapsing             |                         | 2         |               |                 |               |         | 2           |
| Peptic ulcer perforation           |                         | 1         |               |                 |               |         | 1           |

| Event Counts                                                |                         |           |               |                 |               |          |             |
|-------------------------------------------------------------|-------------------------|-----------|---------------|-----------------|---------------|----------|-------------|
| SOC - PT                                                    | mRNA-1273 vs<br>Placebo | mRNA-1273 | mRNA-1273.211 | mRNA-1273.617.2 | mRNA-1273.213 | Placebo  | Grand Total |
| Rectal fissure                                              |                         | 1         |               |                 |               |          | 1           |
| Rectal prolapse                                             |                         | 1         |               |                 |               |          | 1           |
| Rectal ulcer                                                |                         | 1         |               |                 |               |          | 1           |
| Retroperitoneal haematoma                                   |                         | 1         |               |                 |               |          | 1           |
| Retroperitoneal haemorrhage                                 |                         | 2         |               |                 |               |          | 2           |
| Small intestinal obstruction                                | 4                       | 11        |               |                 |               | 1        | 16          |
| Terminal ileitis                                            |                         | 1         |               |                 |               |          | 1           |
| Tooth socket haemorrhage                                    |                         |           |               |                 |               | 1        | 1           |
| Umbilical hernia                                            |                         | 1         |               |                 |               |          | 1           |
| Upper gastrointestinal haemorrhage                          |                         | 3         |               |                 |               |          | 3           |
| Vomiting                                                    | 2                       | 4         |               |                 |               |          | 6           |
| <b>General disorders and administration site conditions</b> | <b>12</b>               | <b>38</b> |               | <b>1</b>        |               | <b>7</b> | <b>58</b>   |
| Asthenia                                                    |                         | 1         |               |                 |               |          | 1           |
| Chest discomfort                                            |                         | 1         |               |                 |               |          | 1           |
| Chest pain                                                  |                         | 10        |               | 1               |               | 2        | 13          |
| Death                                                       | 3                       | 3         |               |                 |               | 1        | 7           |
| Drug withdrawal syndrome                                    |                         | 1         |               |                 |               |          | 1           |
| Fatigue                                                     |                         | 1         |               |                 |               |          | 1           |
| Feeling hot                                                 | 1                       |           |               |                 |               |          | 1           |
| Gait disturbance                                            | 1                       |           |               |                 |               |          | 1           |
| Generalised oedema                                          | 1                       |           |               |                 |               |          | 1           |
| Impaired healing                                            |                         | 1         |               |                 |               |          | 1           |
| Incarcerated hernia                                         | 1                       |           |               |                 |               | 1        | 2           |
| Multiple organ dysfunction syndrome                         | 1                       |           |               |                 |               |          | 1           |
| Necrosis                                                    |                         | 1         |               |                 |               |          | 1           |
| Non-cardiac chest pain                                      | 2                       | 9         |               |                 |               | 1        | 12          |
| Oedema peripheral                                           |                         | 2         |               |                 |               |          | 2           |
| Pain                                                        |                         | 1         |               |                 |               |          | 1           |
| Pyrexia                                                     | 1                       | 2         |               |                 |               |          | 3           |
| Swelling face                                               | 1                       | 2         |               |                 |               |          | 3           |
| Systemic inflammatory response syndrome                     |                         | 2         |               |                 |               | 2        | 4           |
| Vascular stent stenosis                                     |                         | 1         |               |                 |               |          | 1           |
| <b>Hepatobiliary disorders</b>                              | <b>5</b>                | <b>37</b> | <b>3</b>      |                 |               | <b>4</b> | <b>49</b>   |
| Bile duct stone                                             | 1                       | 1         | 1             |                 |               |          | 3           |
| Biliary colic                                               |                         | 2         |               |                 |               |          | 2           |
| Biliary dyskinesia                                          |                         |           |               |                 |               | 1        | 1           |
| Cholecystitis                                               | 3                       | 15        |               |                 |               | 2        | 20          |
| Cholecystitis acute                                         |                         | 4         |               |                 |               | 1        | 5           |
| Cholecystitis chronic                                       |                         | 1         |               |                 |               |          | 1           |
| Cholelithiasis                                              |                         | 8         | 2             |                 |               |          | 10          |
| Cholelithiasis obstructive                                  |                         | 1         |               |                 |               |          | 1           |
| Cholestasis of pregnancy                                    |                         | 1         |               |                 |               |          | 1           |
| Drug-induced liver injury                                   | 1                       |           |               |                 |               |          | 1           |
| Hepatic cirrhosis                                           |                         | 1         |               |                 |               |          | 1           |
| Hepatic failure                                             |                         | 2         |               |                 |               |          | 2           |
| Hepatorenal syndrome                                        |                         | 1         |               |                 |               |          | 1           |
| <b>Immune system disorders</b>                              | <b>1</b>                | <b>13</b> |               |                 |               | <b>2</b> | <b>16</b>   |
| Anaphylactic reaction                                       |                         | 5         |               |                 |               | 1        | 6           |
| Anaphylactic shock                                          |                         | 2         |               |                 |               |          | 2           |

| Event Counts                        |                         |            |               |                 |               |           |             |
|-------------------------------------|-------------------------|------------|---------------|-----------------|---------------|-----------|-------------|
| SOC - PT                            | mRNA-1273 vs<br>Placebo | mRNA-1273  | mRNA-1273.211 | mRNA-1273.617.2 | mRNA-1273.213 | Placebo   | Grand Total |
| Cytokine storm                      | 1                       |            |               |                 |               |           | 1           |
| Drug hypersensitivity               |                         | 4          |               |                 |               |           | 4           |
| Food allergy                        |                         | 1          |               |                 |               |           | 1           |
| Multisystem inflammatory syndrome   |                         |            |               |                 |               | 1         | 1           |
| Solid organ transplant rejection    |                         | 1          |               |                 |               |           | 1           |
| <b>Infections and infestations</b>  | <b>61</b>               | <b>341</b> | <b>5</b>      | <b>2</b>        |               | <b>74</b> | <b>483</b>  |
| Abdominal abscess                   | 1                       | 1          |               |                 |               |           | 2           |
| Abscess limb                        |                         | 3          |               |                 |               |           | 3           |
| Adenovirus infection                | 1                       |            |               |                 |               |           | 1           |
| Appendiceal abscess                 |                         | 1          |               |                 |               |           | 1           |
| Appendicitis                        | 6                       | 28         |               |                 |               | 4         | 38          |
| Appendicitis perforated             |                         | 10         |               |                 |               | 1         | 11          |
| Arthritis bacterial                 |                         | 5          |               |                 |               |           | 5           |
| Bacteraemia                         |                         | 2          |               |                 |               |           | 2           |
| Bacterial sepsis                    |                         | 2          |               |                 |               |           | 2           |
| Biliary sepsis                      |                         | 1          |               |                 |               |           | 1           |
| Breast cellulitis                   |                         | 2          |               |                 |               |           | 2           |
| Bronchiolitis                       | 2                       |            |               |                 |               |           | 2           |
| Bronchitis                          | 1                       | 4          |               |                 |               |           | 5           |
| Cellulitis                          | 1                       | 17         | 1             |                 |               |           | 19          |
| Cellulitis orbital                  | 1                       |            |               |                 |               |           | 1           |
| Cholangitis infective               |                         | 1          |               |                 |               |           | 1           |
| Clostridium bacteraemia             |                         | 1          |               |                 |               |           | 1           |
| Clostridium difficile colitis       |                         | 4          |               |                 |               | 1         | 5           |
| Clostridium difficile infection     | 1                       | 1          |               |                 |               |           | 2           |
| Coccidioidomycosis                  |                         |            |               |                 |               | 1         | 1           |
| Colonic abscess                     |                         | 1          |               |                 |               |           | 1           |
| COVID-19                            | 10                      | 18         |               |                 |               | 29        | 57          |
| COVID-19 pneumonia                  | 1                       | 5          |               |                 |               | 7         | 13          |
| Cystitis                            |                         | 1          |               |                 |               |           | 1           |
| Diabetic foot infection             |                         | 3          |               |                 |               |           | 3           |
| Diverticulitis                      |                         | 20         |               |                 |               | 4         | 24          |
| Enterobacter sepsis                 |                         | 1          |               |                 |               |           | 1           |
| Enterococcal bacteraemia            | 1                       | 1          |               |                 |               |           | 2           |
| Epididymitis                        |                         | 1          |               |                 |               |           | 1           |
| Escherichia urinary tract infection |                         | 3          |               |                 |               |           | 3           |
| Fournier's gangrene                 |                         | 1          |               |                 |               |           | 1           |
| Gangrene                            |                         | 2          | 1             |                 |               |           | 3           |
| Gastroenteritis viral               | 1                       |            |               |                 |               |           | 1           |
| Giardiasis                          |                         | 1          |               |                 |               |           | 1           |
| Groin abscess                       |                         | 1          |               |                 |               |           | 1           |
| Haematoma infection                 |                         | 1          |               |                 |               |           | 1           |
| Hepatitis A                         |                         | 1          |               |                 |               |           | 1           |
| Herpes simplex meningitis           |                         | 1          |               |                 |               |           | 1           |
| Herpes zoster                       |                         | 1          |               |                 |               |           | 1           |
| Implant site infection              |                         | 1          |               |                 |               |           | 1           |
| Infected bite                       |                         | 1          |               |                 |               |           | 1           |
| Infection                           |                         | 1          |               |                 |               |           | 1           |
| Influenza                           |                         | 2          |               |                 |               |           | 2           |

| Event Counts                          |                         |           |               |                 |               |         |             |
|---------------------------------------|-------------------------|-----------|---------------|-----------------|---------------|---------|-------------|
| SOC - PT                              | mRNA-1273 vs<br>Placebo | mRNA-1273 | mRNA-1273.211 | mRNA-1273.617.2 | mRNA-1273.213 | Placebo | Grand Total |
| Joint abscess                         |                         | 1         |               |                 |               |         | 1           |
| Klebsiella bacteraemia                |                         | 1         |               |                 |               |         | 1           |
| Liver abscess                         | 1                       | 3         |               |                 |               |         | 4           |
| Localised infection                   |                         | 1         |               |                 |               | 1       | 2           |
| Lung abscess                          |                         | 1         |               |                 |               |         | 1           |
| Medical device site joint infection   |                         | 1         |               |                 |               |         | 1           |
| Meningitis                            |                         | 1         |               |                 |               |         | 1           |
| Meningitis aseptic                    | 1                       | 1         |               |                 |               |         | 2           |
| Metapneumovirus bronchiolitis         | 1                       |           |               |                 |               |         | 1           |
| Metapneumovirus infection             | 1                       |           |               |                 |               |         | 1           |
| Murine typhus                         | 1                       |           |               |                 |               |         | 1           |
| Nosocomial infection                  |                         | 1         |               |                 |               |         | 1           |
| Oesophageal candidiasis               |                         | 2         |               |                 |               |         | 2           |
| Orchitis                              |                         | 2         |               |                 |               |         | 2           |
| Osteomyelitis                         | 1                       | 7         |               |                 |               |         | 8           |
| Osteomyelitis acute                   |                         |           |               |                 |               | 1       | 1           |
| Osteomyelitis bacterial               |                         | 1         |               |                 |               |         | 1           |
| Osteomyelitis chronic                 |                         | 2         |               |                 |               |         | 2           |
| Pericarditis infective                |                         |           |               |                 |               | 1       | 1           |
| Perineal abscess                      |                         | 1         |               |                 |               |         | 1           |
| Perirectal abscess                    | 1                       | 2         |               |                 |               |         | 3           |
| Peritoneal abscess                    |                         | 1         |               |                 |               |         | 1           |
| Peritonitis                           |                         | 3         |               |                 |               |         | 3           |
| Pharyngitis streptococcal             | 1                       |           |               |                 |               |         | 1           |
| Pneumonia                             | 8                       | 47        |               |                 |               | 7       | 62          |
| Pneumonia aspiration                  |                         | 3         |               |                 |               | 1       | 4           |
| Pneumonia bacterial                   | 1                       | 4         |               |                 |               |         | 5           |
| Pneumonia klebsiella                  |                         |           |               |                 |               | 1       | 1           |
| Pneumonia legionella                  |                         |           |               | 1               |               |         | 1           |
| Pneumonia mycoplasmal                 |                         | 1         |               |                 |               |         | 1           |
| Pneumonia parainfluenzae viral        |                         | 1         |               |                 |               |         | 1           |
| Pneumonia respiratory syncytial viral |                         | 1         |               |                 |               |         | 1           |
| Pneumonia staphylococcal              |                         | 1         |               |                 |               |         | 1           |
| Pneumonia viral                       | 1                       |           |               |                 |               |         | 1           |
| Post procedural cellulitis            |                         | 1         |               |                 |               |         | 1           |
| Post procedural infection             |                         | 4         |               |                 |               | 1       | 5           |
| Post-acute COVID-19 syndrome          | 1                       |           |               |                 |               |         | 1           |
| Postoperative abscess                 |                         | 2         |               |                 |               |         | 2           |
| Postoperative wound infection         |                         | 6         |               |                 |               |         | 6           |
| Pyelonephritis                        | 1                       | 4         |               |                 |               | 2       | 7           |
| Pyelonephritis acute                  | 1                       | 2         |               |                 |               |         | 3           |
| Respiratory syncytial virus infection |                         | 1         |               |                 |               |         | 1           |
| Rhinovirus infection                  | 2                       | 2         |               |                 |               |         | 4           |
| Salpingitis                           | 1                       |           |               |                 |               |         | 1           |
| Sepsis                                |                         | 33        |               |                 |               | 4       | 37          |
| Septic shock                          | 2                       | 6         |               | 1               |               | 2       | 11          |
| Shigella sepsis                       |                         | 1         |               |                 |               |         | 1           |
| Sialoadenitis                         |                         | 1         |               |                 |               |         | 1           |
| Sinusitis                             |                         | 1         |               |                 |               |         | 1           |

| Event Counts                                          |                         |            |               |                 |               |           |             |
|-------------------------------------------------------|-------------------------|------------|---------------|-----------------|---------------|-----------|-------------|
| SOC - PT                                              | mRNA-1273 vs<br>Placebo | mRNA-1273  | mRNA-1273.211 | mRNA-1273.617.2 | mRNA-1273.213 | Placebo   | Grand Total |
| Spinal cord abscess                                   |                         | 1          |               |                 |               |           | 1           |
| Staphylococcal bacteraemia                            |                         | 3          |               |                 |               |           | 3           |
| Staphylococcal infection                              |                         | 3          |               |                 |               |           | 3           |
| Staphylococcal sepsis                                 |                         | 1          |               |                 |               |           | 1           |
| Streptococcal bacteraemia                             |                         | 1          |               |                 |               |           | 1           |
| Streptococcal endocarditis                            |                         | 1          |               |                 |               |           | 1           |
| Streptococcal infection                               |                         | 1          |               |                 |               |           | 1           |
| Streptococcal sepsis                                  | 1                       |            |               |                 |               |           | 1           |
| Subcutaneous abscess                                  |                         |            |               |                 |               | 1         | 1           |
| Tonsillitis                                           |                         | 2          |               |                 |               |           | 2           |
| Tooth abscess                                         | 1                       | 1          |               |                 |               |           | 2           |
| Toxic shock syndrome                                  | 1                       |            |               |                 |               |           | 1           |
| Upper respiratory tract infection                     |                         | 2          |               |                 |               |           | 2           |
| Urinary tract infection                               | 1                       | 15         | 2             |                 |               | 5         | 23          |
| Urinary tract infection bacterial                     | 1                       |            |               |                 |               |           | 1           |
| Urinary tract infection pseudomonal                   |                         | 1          |               |                 |               |           | 1           |
| Urosepsis                                             | 2                       | 3          | 1             |                 |               |           | 6           |
| Viral pharyngitis                                     | 1                       |            |               |                 |               |           | 1           |
| Wound infection                                       |                         | 1          |               |                 |               |           | 1           |
| <b>Injury, poisoning and procedural complications</b> | <b>31</b>               | <b>151</b> | <b>1</b>      |                 |               | <b>29</b> | <b>212</b>  |
| Accidental overdose                                   |                         | 3          |               |                 |               |           | 3           |
| Acetabulum fracture                                   |                         | 2          |               |                 |               |           | 2           |
| Alcohol poisoning                                     |                         | 1          |               |                 |               |           | 1           |
| Anaemia postoperative                                 |                         |            |               |                 |               | 2         | 2           |
| Animal bite                                           |                         | 3          |               |                 |               |           | 3           |
| Ankle fracture                                        | 1                       | 6          |               |                 |               | 1         | 8           |
| Avulsion fracture                                     |                         | 1          |               |                 |               |           | 1           |
| Back injury                                           | 1                       |            |               |                 |               |           | 1           |
| Brain herniation                                      |                         | 1          |               |                 |               |           | 1           |
| Cartilage injury                                      | 1                       |            |               |                 |               |           | 1           |
| Cervical vertebral fracture                           |                         | 5          |               |                 |               |           | 5           |
| Clavicle fracture                                     | 1                       |            |               |                 |               |           | 1           |
| Concussion                                            | 1                       | 2          |               |                 |               |           | 3           |
| Contusion                                             |                         | 1          |               |                 |               |           | 1           |
| Craniocerebral injury                                 |                         | 4          |               |                 |               |           | 4           |
| Cystitis radiation                                    |                         | 1          |               |                 |               |           | 1           |
| Exposure to toxic agent                               |                         | 1          |               |                 |               |           | 1           |
| Eye injury                                            |                         | 1          |               |                 |               |           | 1           |
| Facial bones fracture                                 | 1                       | 1          |               |                 |               |           | 2           |
| Fall                                                  | 1                       | 4          |               |                 |               | 4         | 9           |
| Femoral neck fracture                                 | 1                       | 1          |               |                 |               |           | 2           |
| Femur fracture                                        | 1                       | 8          |               |                 |               | 3         | 12          |
| Fibula fracture                                       |                         | 3          |               |                 |               |           | 3           |
| Foot fracture                                         |                         | 2          |               |                 |               |           | 2           |
| Foreign body in gastrointestinal tract                |                         | 1          |               |                 |               |           | 1           |
| Foreign body ingestion                                |                         | 2          |               |                 |               |           | 2           |
| Fracture displacement                                 |                         | 1          |               |                 |               |           | 1           |
| Fractured sacrum                                      |                         | 1          |               |                 |               |           | 1           |
| Gastrointestinal procedural complication              |                         | 1          |               |                 |               |           | 1           |

| Event Counts                       |                         |           |               |                 |               |         |             |
|------------------------------------|-------------------------|-----------|---------------|-----------------|---------------|---------|-------------|
| SOC - PT                           | mRNA-1273 vs<br>Placebo | mRNA-1273 | mRNA-1273.211 | mRNA-1273.617.2 | mRNA-1273.213 | Placebo | Grand Total |
| Gun shot wound                     |                         | 2         |               |                 |               | 1       | 3           |
| Head injury                        | 2                       | 4         |               |                 |               |         | 6           |
| Hip fracture                       | 2                       | 7         | 1             |                 |               | 1       | 11          |
| Humerus fracture                   |                         | 1         |               |                 |               |         | 1           |
| Incarcerated incisional hernia     | 1                       |           |               |                 |               |         | 1           |
| Incision site pain                 | 1                       |           |               |                 |               | 1       | 2           |
| Incisional hernia                  |                         | 1         |               |                 |               |         | 1           |
| Incisional hernia, obstructive     |                         | 1         |               |                 |               |         | 1           |
| Injury                             |                         | 1         |               |                 |               |         | 1           |
| Joint dislocation                  |                         | 1         |               |                 |               |         | 1           |
| Joint injury                       |                         | 1         |               |                 |               | 2       | 3           |
| Ligament rupture                   |                         | 1         |               |                 |               |         | 1           |
| Limb injury                        |                         | 2         |               |                 |               |         | 2           |
| Lower limb fracture                |                         | 1         |               |                 |               |         | 1           |
| Lumbar vertebral fracture          |                         | 1         |               |                 |               |         | 1           |
| Maternal exposure before pregnancy |                         | 1         |               |                 |               |         | 1           |
| Meniscus injury                    |                         | 1         |               |                 |               |         | 1           |
| Overdose                           | 1                       | 2         |               |                 |               |         | 3           |
| Patella fracture                   |                         | 1         |               |                 |               |         | 1           |
| Pelvic fracture                    |                         | 1         |               |                 |               | 1       | 2           |
| Post procedural complication       |                         | 2         |               |                 |               |         | 2           |
| Post procedural fever              | 1                       | 1         |               |                 |               | 1       | 3           |
| Post procedural haematoma          | 1                       | 1         |               |                 |               |         | 2           |
| Post procedural haemorrhage        | 1                       | 1         |               |                 |               |         | 2           |
| Post procedural hypotension        |                         | 1         |               |                 |               |         | 1           |
| Procedural haemorrhage             |                         | 1         |               |                 |               | 1       | 2           |
| Procedural nausea                  | 1                       | 1         |               |                 |               |         | 2           |
| Procedural pain                    |                         | 1         |               |                 |               |         | 1           |
| Radius fracture                    |                         | 1         |               |                 |               |         | 1           |
| Rib fracture                       |                         | 6         |               |                 |               | 3       | 9           |
| Road traffic accident              | 2                       | 8         |               |                 |               | 1       | 11          |
| Seroma                             |                         | 2         |               |                 |               |         | 2           |
| Skin laceration                    | 1                       | 6         |               |                 |               |         | 7           |
| Snake bite                         |                         | 1         |               |                 |               |         | 1           |
| Spinal cord injury cervical        |                         | 1         |               |                 |               |         | 1           |
| Splenic injury                     |                         |           |               |                 |               | 1       | 1           |
| Stab wound                         |                         |           |               |                 |               | 1       | 1           |
| Sternal fracture                   |                         | 2         |               |                 |               | 1       | 3           |
| Struck by lightning                |                         | 1         |               |                 |               |         | 1           |
| Subdural haematoma                 |                         | 5         |               |                 |               |         | 5           |
| Sunburn                            | 1                       |           |               |                 |               |         | 1           |
| Superficial injury of eye          | 1                       |           |               |                 |               |         | 1           |
| Tendon injury                      |                         | 1         |               |                 |               |         | 1           |
| Tendon rupture                     | 1                       | 4         |               |                 |               | 1       | 6           |
| Thoracic vertebral fracture        | 1                       | 1         |               |                 |               |         | 2           |
| Tibia fracture                     |                         | 5         |               |                 |               | 1       | 6           |
| Toxicity to various agents         | 2                       | 1         |               |                 |               |         | 3           |
| Tracheal haemorrhage               | 1                       |           |               |                 |               |         | 1           |
| Traumatic fracture                 |                         | 2         |               |                 |               |         | 2           |



| Event Counts                                           |                      |            |               |                 |               |           |             |
|--------------------------------------------------------|----------------------|------------|---------------|-----------------|---------------|-----------|-------------|
| SOC - PT                                               | mRNA-1273 vs Placebo | mRNA-1273  | mRNA-1273.211 | mRNA-1273.617.2 | mRNA-1273.213 | Placebo   | Grand Total |
| Traumatic haemothorax                                  |                      |            |               |                 |               | 2         | 2           |
| Traumatic liver injury                                 |                      | 1          |               |                 |               |           | 1           |
| Upper limb fracture                                    |                      | 1          |               |                 |               |           | 1           |
| Vulvovaginal injury                                    |                      | 1          |               |                 |               |           | 1           |
| Wound dehiscence                                       |                      | 3          |               |                 |               |           | 3           |
| Wrist fracture                                         | 1                    | 2          |               |                 |               |           | 3           |
| <b>Investigations</b>                                  |                      | <b>11</b>  | <b>1</b>      |                 |               | <b>1</b>  | <b>13</b>   |
| Ammonia increased                                      |                      | 1          |               |                 |               |           | 1           |
| Anticoagulation drug level above therapeutic           |                      | 1          |               |                 |               |           | 1           |
| Bacterial test positive                                |                      | 1          |               |                 |               |           | 1           |
| Ejection fraction decreased                            |                      | 1          |               |                 |               |           | 1           |
| Heart rate decreased                                   |                      | 1          |               |                 |               |           | 1           |
| Hepatic enzyme increased                               |                      | 2          |               |                 |               |           | 2           |
| Liver function test increased                          |                      | 1          |               |                 |               |           | 1           |
| Myocardial necrosis marker increased                   |                      | 1          | 1             |                 |               |           | 2           |
| Platelet count decreased                               |                      | 1          |               |                 |               |           | 1           |
| Transaminases increased                                |                      |            |               |                 |               | 1         | 1           |
| Weight increased                                       |                      | 1          |               |                 |               |           | 1           |
| <b>Metabolism and nutrition disorders</b>              | <b>9</b>             | <b>63</b>  | <b>1</b>      |                 |               | <b>13</b> | <b>86</b>   |
| Dehydration                                            | 1                    | 8          | 1             |                 |               | 4         | 14          |
| Diabetes mellitus                                      |                      | 1          |               |                 |               |           | 1           |
| Diabetes mellitus inadequate control                   |                      | 1          |               |                 |               | 1         | 2           |
| Diabetic complication                                  | 1                    |            |               |                 |               |           | 1           |
| Diabetic ketoacidosis                                  | 2                    | 7          |               |                 |               | 2         | 11          |
| Electrolyte imbalance                                  | 1                    | 1          |               |                 |               |           | 2           |
| Euglycaemic diabetic ketoacidosis                      |                      | 1          |               |                 |               |           | 1           |
| Failure to thrive                                      |                      | 1          |               |                 |               |           | 1           |
| Gout                                                   | 1                    | 2          |               |                 |               |           | 3           |
| Hypercalcaemia                                         |                      | 1          |               |                 |               |           | 1           |
| Hypercholesterolaemia                                  |                      | 1          |               |                 |               |           | 1           |
| Hyperglycaemia                                         |                      | 2          |               |                 |               |           | 2           |
| Hyperglycaemic hyperosmolar nonketotic syndrome        |                      | 1          |               |                 |               |           | 1           |
| Hyperkalaemia                                          |                      | 4          |               |                 |               |           | 4           |
| Hypochloraemia                                         |                      | 1          |               |                 |               |           | 1           |
| Hypoglycaemia                                          | 1                    | 1          |               |                 |               | 1         | 3           |
| Hypokalaemia                                           |                      | 2          |               |                 |               | 1         | 3           |
| Hypomagnesaemia                                        |                      | 1          |               |                 |               | 1         | 2           |
| Hyponatraemia                                          |                      | 7          |               |                 |               | 1         | 8           |
| Ketoacidosis                                           |                      | 1          |               |                 |               |           | 1           |
| Lactic acidosis                                        |                      | 3          |               |                 |               |           | 3           |
| Metabolic acidosis                                     | 1                    | 2          |               |                 |               |           | 3           |
| Obesity                                                |                      | 9          |               |                 |               |           | 9           |
| Type 1 diabetes mellitus                               | 1                    | 3          |               |                 |               |           | 4           |
| Type 2 diabetes mellitus                               |                      | 2          |               |                 |               | 2         | 4           |
| <b>Musculoskeletal and connective tissue disorders</b> | <b>19</b>            | <b>150</b> | <b>2</b>      | <b>1</b>        |               | <b>28</b> | <b>200</b>  |
| Ankylosing spondylitis                                 |                      | 1          |               |                 |               |           | 1           |
| Arthralgia                                             |                      | 5          |               |                 |               |           | 5           |
| Arthritis                                              | 1                    | 2          |               |                 |               |           | 3           |
| Back pain                                              | 1                    | 8          |               |                 |               |           | 9           |

| Event Counts                                                               |                         |            |               |                 |               |           |             |
|----------------------------------------------------------------------------|-------------------------|------------|---------------|-----------------|---------------|-----------|-------------|
| SOC - PT                                                                   | mRNA-1273 vs<br>Placebo | mRNA-1273  | mRNA-1273.211 | mRNA-1273.617.2 | mRNA-1273.213 | Placebo   | Grand Total |
| Bursitis                                                                   |                         | 1          |               |                 |               |           | 1           |
| Cervical spinal stenosis                                                   |                         | 2          |               |                 |               | 1         | 3           |
| Chondrocalcinosis pyrophosphate                                            |                         | 1          |               |                 |               |           | 1           |
| Connective tissue disorder                                                 |                         | 1          |               |                 |               |           | 1           |
| Costochondritis                                                            |                         | 1          |               |                 |               |           | 1           |
| Flank pain                                                                 | 1                       | 1          |               |                 |               |           | 2           |
| Foot deformity                                                             |                         | 3          |               |                 |               |           | 3           |
| Fracture nonunion                                                          | 1                       |            |               |                 |               |           | 1           |
| Intervertebral disc degeneration                                           |                         | 6          |               |                 |               | 1         | 7           |
| Intervertebral disc disorder                                               |                         | 1          |               |                 |               |           | 1           |
| Intervertebral disc protrusion                                             | 1                       | 4          |               |                 |               | 4         | 9           |
| Joint swelling                                                             |                         | 1          |               |                 |               |           | 1           |
| Lumbar spinal stenosis                                                     |                         | 7          |               |                 |               |           | 7           |
| Muscle spasms                                                              |                         | 1          |               |                 |               |           | 1           |
| Muscular weakness                                                          | 1                       | 3          |               |                 |               |           | 4           |
| Musculoskeletal chest pain                                                 | 1                       | 3          |               |                 |               | 2         | 6           |
| Myositis                                                                   |                         | 1          |               |                 |               |           | 1           |
| Neck pain                                                                  | 1                       | 4          |               | 1               |               |           | 6           |
| Osteoarthritis                                                             | 2                       | 65         | 2             |                 |               | 16        | 85          |
| Osteonecrosis                                                              |                         | 2          |               |                 |               | 1         | 3           |
| Pain in extremity                                                          | 1                       |            |               |                 |               |           | 1           |
| Pseudarthrosis                                                             |                         | 1          |               |                 |               |           | 1           |
| Rhabdomyolysis                                                             | 1                       | 3          |               |                 |               |           | 4           |
| Rheumatoid arthritis                                                       |                         | 1          |               |                 |               |           | 1           |
| Soft tissue disorder                                                       |                         | 1          |               |                 |               |           | 1           |
| Spinal instability                                                         |                         | 1          |               |                 |               |           | 1           |
| Spinal osteoarthritis                                                      | 1                       | 6          |               |                 |               | 2         | 9           |
| Spinal stenosis                                                            | 4                       | 2          |               |                 |               | 1         | 7           |
| Spinal synovial cyst                                                       |                         | 2          |               |                 |               |           | 2           |
| Spondylolisthesis                                                          | 1                       | 6          |               |                 |               |           | 7           |
| Tendon disorder                                                            |                         | 1          |               |                 |               |           | 1           |
| Tenosynovitis                                                              |                         | 2          |               |                 |               |           | 2           |
| Vertebral foraminal stenosis                                               | 1                       |            |               |                 |               |           | 1           |
| <b>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</b> | <b>6</b>                | <b>155</b> | <b>2</b>      |                 |               | <b>27</b> | <b>190</b>  |
| Adenocarcinoma gastric                                                     |                         |            |               |                 |               | 1         | 1           |
| Adenocarcinoma of colon                                                    |                         | 1          |               |                 |               |           | 1           |
| Anaplastic large-cell lymphoma                                             |                         | 1          |               |                 |               |           | 1           |
| B-cell lymphoma                                                            |                         | 2          |               |                 |               |           | 2           |
| B-cell small lymphocytic lymphoma                                          |                         | 1          |               |                 |               |           | 1           |
| Benign lung neoplasm                                                       |                         | 1          |               |                 |               |           | 1           |
| Benign neoplasm of thymus                                                  |                         | 1          |               |                 |               |           | 1           |
| Bladder cancer                                                             |                         | 1          |               |                 |               |           | 1           |
| Bladder cancer recurrent                                                   |                         | 1          |               |                 |               |           | 1           |
| Bone cancer metastatic                                                     |                         | 1          |               |                 |               |           | 1           |
| Borderline mucinous tumour of ovary                                        |                         | 1          |               |                 |               |           | 1           |
| Breast cancer                                                              |                         | 3          | 1             |                 |               | 1         | 5           |
| Breast cancer female                                                       |                         | 1          |               |                 |               |           | 1           |
| Breast cancer stage I                                                      | 1                       | 2          |               |                 |               |           | 3           |
| Cancer pain                                                                |                         | 1          |               |                 |               |           | 1           |

| Event Counts                                   |                         |           |               |                 |               |         |             |
|------------------------------------------------|-------------------------|-----------|---------------|-----------------|---------------|---------|-------------|
| SOC - PT                                       | mRNA-1273 vs<br>Placebo | mRNA-1273 | mRNA-1273.211 | mRNA-1273.617.2 | mRNA-1273.213 | Placebo | Grand Total |
| Clear cell renal cell carcinoma                |                         | 4         |               |                 |               | 1       | 5           |
| Colon adenoma                                  |                         | 1         |               |                 |               |         | 1           |
| Colon cancer                                   |                         | 6         |               |                 |               |         | 6           |
| Colon cancer stage III                         | 1                       |           |               |                 |               |         | 1           |
| Colorectal cancer                              |                         | 2         |               |                 |               |         | 2           |
| Colorectal cancer metastatic                   |                         |           |               |                 |               | 1       | 1           |
| Diffuse large B-cell lymphoma stage IV         |                         | 1         |               |                 |               |         | 1           |
| Endometrial adenocarcinoma                     |                         |           |               |                 |               | 1       | 1           |
| Endometrial cancer                             |                         | 1         |               |                 |               | 3       | 4           |
| Follicular lymphoma                            |                         | 1         |               |                 |               |         | 1           |
| Gallbladder neoplasm                           |                         | 1         |               |                 |               |         | 1           |
| Gastric cancer                                 | 1                       | 2         |               |                 |               |         | 3           |
| Gastric cancer stage III                       |                         | 1         |               |                 |               |         | 1           |
| Gastrointestinal stromal tumour                |                         | 1         |               |                 |               |         | 1           |
| Glioblastoma multiforme                        |                         | 1         |               |                 |               |         | 1           |
| Hepatocellular carcinoma                       | 2                       | 1         |               |                 |               |         | 3           |
| High-grade B-cell lymphoma                     |                         | 1         |               |                 |               |         | 1           |
| Hodgkin's disease                              |                         | 1         |               |                 |               |         | 1           |
| Intraductal proliferative breast lesion        |                         | 3         | 1             |                 |               | 3       | 7           |
| Invasive ductal breast carcinoma               |                         | 5         |               |                 |               | 2       | 7           |
| Invasive lobular breast carcinoma              |                         | 1         |               |                 |               |         | 1           |
| Langerhans' cell histiocytosis                 |                         | 1         |               |                 |               |         | 1           |
| Leiomyosarcoma metastatic                      |                         |           |               |                 |               | 1       | 1           |
| Lentigo maligna                                |                         | 1         |               |                 |               |         | 1           |
| Liposarcoma                                    |                         | 1         |               |                 |               |         | 1           |
| Lung adenocarcinoma                            |                         | 2         |               |                 |               | 1       | 3           |
| Lung adenocarcinoma stage IV                   |                         | 1         |               |                 |               |         | 1           |
| Lung cancer metastatic                         |                         | 1         |               |                 |               |         | 1           |
| Lung carcinoma cell type unspecified stage III |                         | 1         |               |                 |               |         | 1           |
| Malignant ascites                              |                         | 1         |               |                 |               |         | 1           |
| Malignant melanoma                             |                         | 7         |               |                 |               |         | 7           |
| Malignant melanoma stage III                   |                         | 1         |               |                 |               |         | 1           |
| Malignant neoplasm of thymus                   |                         | 1         |               |                 |               |         | 1           |
| Meningioma                                     |                         | 2         |               |                 |               |         | 2           |
| Metastases to lung                             |                         | 2         |               |                 |               |         | 2           |
| Metastatic renal cell carcinoma                |                         | 1         |               |                 |               |         | 1           |
| Myxofibrosarcoma                               |                         | 1         |               |                 |               |         | 1           |
| Neoplasm malignant                             |                         | 1         |               |                 |               |         | 1           |
| Neoplasm of orbit                              |                         | 1         |               |                 |               |         | 1           |
| Neuroendocrine carcinoma                       |                         | 1         |               |                 |               |         | 1           |
| Neuroendocrine carcinoma metastatic            |                         | 1         |               |                 |               |         | 1           |
| Non-Hodgkin's lymphoma                         |                         | 1         |               |                 |               |         | 1           |
| Non-small cell lung cancer                     |                         | 1         |               |                 |               | 1       | 2           |
| Oesophageal adenocarcinoma                     |                         | 1         |               |                 |               |         | 1           |
| Oesophageal carcinoma                          |                         | 3         |               |                 |               |         | 3           |
| Osteoma                                        |                         | 1         |               |                 |               |         | 1           |
| Ovarian clear cell carcinoma                   |                         | 1         |               |                 |               |         | 1           |
| Pancreatic carcinoma                           |                         | 5         |               |                 |               |         | 5           |
| Pancreatic carcinoma metastatic                |                         | 2         |               |                 |               | 1       | 3           |

| Event Counts                               |                         |            |               |                 |               |           |             |
|--------------------------------------------|-------------------------|------------|---------------|-----------------|---------------|-----------|-------------|
| SOC - PT                                   | mRNA-1273 vs<br>Placebo | mRNA-1273  | mRNA-1273.211 | mRNA-1273.617.2 | mRNA-1273.213 | Placebo   | Grand Total |
| Pancreatic carcinoma stage IV              |                         | 1          |               |                 |               | 1         | 2           |
| Papillary renal cell carcinoma             |                         | 1          |               |                 |               |           | 1           |
| Papillary thyroid cancer                   |                         | 2          |               |                 |               | 1         | 3           |
| Paranasal sinus neoplasm                   |                         | 1          |               |                 |               |           | 1           |
| Pelvic neoplasm                            |                         | 1          |               |                 |               |           | 1           |
| Phaeochromocytoma                          |                         | 1          |               |                 |               |           | 1           |
| Pituitary tumour benign                    |                         | 1          |               |                 |               |           | 1           |
| Plasma cell myeloma                        |                         | 1          |               |                 |               |           | 1           |
| Pleomorphic malignant fibrous histiocytoma |                         | 1          |               |                 |               |           | 1           |
| Prolactin-producing pituitary tumour       |                         | 1          |               |                 |               |           | 1           |
| Prostate cancer                            |                         | 20         |               |                 |               | 4         | 24          |
| Prostate cancer metastatic                 |                         | 3          |               |                 |               | 1         | 4           |
| Prostate cancer recurrent                  |                         | 1          |               |                 |               |           | 1           |
| Prostate cancer stage II                   |                         | 1          |               |                 |               |           | 1           |
| Renal cancer                               |                         | 1          |               |                 |               |           | 1           |
| Renal cell carcinoma                       | 1                       |            |               |                 |               | 1         | 2           |
| Salivary gland cancer stage IV             |                         | 1          |               |                 |               |           | 1           |
| Sarcoma                                    |                         | 1          |               |                 |               |           | 1           |
| Schwannoma                                 |                         | 1          |               |                 |               |           | 1           |
| Small cell lung cancer metastatic          |                         | 1          |               |                 |               |           | 1           |
| Splenic marginal zone lymphoma             |                         | 1          |               |                 |               |           | 1           |
| Squamous cell carcinoma                    |                         | 2          |               |                 |               |           | 2           |
| Squamous cell carcinoma of skin            |                         | 1          |               |                 |               |           | 1           |
| Squamous cell carcinoma of the tongue      |                         | 1          |               |                 |               |           | 1           |
| T-cell type acute leukaemia                |                         | 1          |               |                 |               |           | 1           |
| Throat cancer                              |                         | 1          |               |                 |               |           | 1           |
| Thymoma                                    |                         | 1          |               |                 |               |           | 1           |
| Thymoma malignant                          |                         | 1          |               |                 |               |           | 1           |
| Thyroid cancer                             |                         | 1          |               |                 |               | 1         | 2           |
| Thyroid cancer metastatic                  |                         | 1          |               |                 |               |           | 1           |
| Tonsil cancer                              |                         | 1          |               |                 |               |           | 1           |
| Uterine cancer                             |                         | 2          |               |                 |               |           | 2           |
| Uterine leiomyoma                          |                         | 5          |               |                 |               | 1         | 6           |
| <b>Nervous system disorders</b>            | <b>20</b>               | <b>140</b> | <b>4</b>      |                 | <b>1</b>      | <b>19</b> | <b>184</b>  |
| Altered state of consciousness             |                         | 1          |               |                 |               |           | 1           |
| Amnesia                                    |                         | 1          |               |                 |               |           | 1           |
| Amyotrophic lateral sclerosis              | 1                       | 1          |               |                 |               |           | 2           |
| Arachnoid cyst                             |                         |            |               |                 |               | 1         | 1           |
| Ataxia                                     |                         | 1          |               |                 |               |           | 1           |
| Autonomic nervous system imbalance         |                         | 1          |               |                 |               |           | 1           |
| Balance disorder                           |                         | 1          |               |                 |               |           | 1           |
| Basal ganglia haemorrhage                  | 1                       |            |               |                 |               |           | 1           |
| Bell's palsy                               |                         | 2          |               |                 |               |           | 2           |
| Brain stem haemorrhage                     |                         | 1          |               |                 |               |           | 1           |
| Brain stem infarction                      |                         | 1          |               |                 |               |           | 1           |
| Carotid artery occlusion                   |                         | 1          |               |                 |               |           | 1           |
| Carotid artery stenosis                    |                         | 5          |               |                 |               |           | 5           |
| Carotid artery thrombosis                  |                         | 1          |               |                 |               |           | 1           |
| Cauda equina syndrome                      | 1                       |            |               |                 |               |           | 1           |

| Event Counts                  |                      |           |               |                 |               |         |             |
|-------------------------------|----------------------|-----------|---------------|-----------------|---------------|---------|-------------|
| SOC - PT                      | mRNA-1273 vs Placebo | mRNA-1273 | mRNA-1273.211 | mRNA-1273.617.2 | mRNA-1273.213 | Placebo | Grand Total |
| Cerebellar haemorrhage        |                      | 1         |               |                 |               |         | 1           |
| Cerebral infarction           |                      | 1         |               |                 |               |         | 1           |
| Cerebrospinal fluid leakage   |                      | 1         |               |                 |               |         | 1           |
| Cerebrovascular accident      | 5                    | 22        |               |                 | 1             | 2       | 30          |
| Cervical cord compression     |                      | 1         |               |                 |               |         | 1           |
| Cervical radiculopathy        |                      | 1         |               |                 |               |         | 1           |
| Dizziness                     |                      | 2         | 1             |                 |               | 1       | 4           |
| Drug withdrawal convulsions   |                      | 1         |               |                 |               |         | 1           |
| Embolitic stroke              |                      | 3         |               |                 |               |         | 3           |
| Encephalopathy                |                      | 2         |               |                 |               | 1       | 3           |
| Essential tremor              |                      | 1         |               |                 |               |         | 1           |
| Febrile convulsion            | 1                    | 1         |               |                 |               |         | 2           |
| Foetal movement disorder      |                      | 1         |               |                 |               |         | 1           |
| Guillain-Barre syndrome       |                      | 1         |               |                 |               |         | 1           |
| Haemorrhage intracranial      |                      | 1         |               |                 |               |         | 1           |
| Haemorrhagic stroke           |                      |           |               |                 |               | 1       | 1           |
| Headache                      |                      | 1         |               |                 |               |         | 1           |
| Hemiparesis                   | 1                    |           |               |                 |               | 1       | 2           |
| Hemiplegic migraine           |                      | 1         |               |                 |               |         | 1           |
| Hydrocephalus                 | 1                    |           |               |                 |               |         | 1           |
| Hypoaesthesia                 |                      | 2         |               |                 |               |         | 2           |
| Idiopathic partial epilepsy   |                      | 1         |               |                 |               |         | 1           |
| Intracranial aneurysm         |                      | 1         |               |                 |               |         | 1           |
| Ischaemic cerebral infarction |                      | 1         |               |                 |               |         | 1           |
| Ischaemic stroke              |                      | 1         |               |                 |               | 1       | 2           |
| Lacunar stroke                |                      | 1         |               |                 |               |         | 1           |
| Lumbar radiculopathy          |                      | 4         |               |                 |               |         | 4           |
| Migraine                      | 1                    |           |               |                 |               |         | 1           |
| Multiple sclerosis            |                      | 1         |               |                 |               | 1       | 2           |
| Myasthenia gravis             |                      | 1         |               |                 |               |         | 1           |
| Myelopathy                    |                      | 2         |               |                 |               |         | 2           |
| Nerve compression             |                      | 1         |               |                 |               | 1       | 2           |
| Nervous system cyst           |                      | 1         |               |                 |               |         | 1           |
| Optic neuritis                |                      | 1         |               |                 |               |         | 1           |
| Paraesthesia                  | 2                    | 2         |               |                 |               |         | 4           |
| Paralysis                     |                      | 1         |               |                 |               |         | 1           |
| Presyncope                    |                      | 4         |               |                 |               |         | 4           |
| Radiculopathy                 | 1                    |           |               |                 |               |         | 1           |
| Ruptured cerebral aneurysm    |                      | 1         |               |                 |               |         | 1           |
| Sciatica                      |                      | 2         |               |                 |               |         | 2           |
| Seizure                       | 2                    | 7         |               |                 |               |         | 9           |
| Seizure like phenomena        |                      | 1         |               |                 |               |         | 1           |
| Speech disorder               |                      | 1         |               |                 |               | 1       | 2           |
| Spinal claudication           |                      | 2         |               |                 |               |         | 2           |
| Spinal cord compression       |                      | 2         |               |                 |               |         | 2           |
| Subarachnoid haemorrhage      | 1                    | 4         |               |                 |               |         | 5           |
| Syncope                       | 2                    | 20        | 1             |                 |               | 5       | 28          |
| Thalamic infarction           |                      | 1         |               |                 |               |         | 1           |
| Toxic encephalopathy          |                      | 1         |               |                 |               |         | 1           |

| Event Counts                                          |                         |           |               |                 |               |           |             |
|-------------------------------------------------------|-------------------------|-----------|---------------|-----------------|---------------|-----------|-------------|
| SOC - PT                                              | mRNA-1273 vs<br>Placebo | mRNA-1273 | mRNA-1273.211 | mRNA-1273.617.2 | mRNA-1273.213 | Placebo   | Grand Total |
| Transient global amnesia                              |                         | 2         |               |                 |               |           | 2           |
| Transient ischaemic attack                            |                         | 9         | 2             |                 |               | 2         | 13          |
| Tremor                                                |                         | 1         |               |                 |               |           | 1           |
| Trigeminal neuralgia                                  |                         | 1         |               |                 |               | 1         | 2           |
| Unresponsive to stimuli                               |                         | 1         |               |                 |               |           | 1           |
| <b>Pregnancy, puerperium and perinatal conditions</b> | <b>4</b>                | <b>30</b> |               |                 |               | <b>2</b>  | <b>36</b>   |
| Abortion missed                                       |                         | 1         |               |                 |               |           | 1           |
| Abortion spontaneous                                  | 3                       | 15        |               |                 |               | 2         | 20          |
| Delivery                                              |                         | 1         |               |                 |               |           | 1           |
| Ectopic pregnancy                                     | 1                       | 1         |               |                 |               |           | 2           |
| Foetal death                                          |                         | 1         |               |                 |               |           | 1           |
| Hyperemesis gravidarum                                |                         | 1         |               |                 |               |           | 1           |
| Morning sickness                                      |                         | 2         |               |                 |               |           | 2           |
| Pre-eclampsia                                         |                         | 5         |               |                 |               |           | 5           |
| Pregnancy                                             |                         | 1         |               |                 |               |           | 1           |
| Premature rupture of membranes                        |                         | 1         |               |                 |               |           | 1           |
| Prolonged pregnancy                                   |                         | 1         |               |                 |               |           | 1           |
| <b>Product issues</b>                                 | <b>1</b>                | <b>4</b>  |               |                 |               |           | <b>5</b>    |
| Device dislocation                                    |                         | 1         |               |                 |               |           | 1           |
| Device electrical impedance issue                     |                         | 1         |               |                 |               |           | 1           |
| Device failure                                        |                         | 1         |               |                 |               |           | 1           |
| Device loosening                                      |                         | 1         |               |                 |               |           | 1           |
| Lead dislodgement                                     | 1                       |           |               |                 |               |           | 1           |
| <b>Psychiatric disorders</b>                          | <b>29</b>               | <b>55</b> |               |                 |               | <b>12</b> | <b>96</b>   |
| Affective disorder                                    | 1                       |           |               |                 |               |           | 1           |
| Agitation                                             |                         |           |               |                 |               | 1         | 1           |
| Alcohol abuse                                         | 1                       |           |               |                 |               |           | 1           |
| Alcohol use disorder                                  |                         | 1         |               |                 |               |           | 1           |
| Alcohol withdrawal syndrome                           | 2                       | 2         |               |                 |               | 1         | 5           |
| Alcoholism                                            |                         |           |               |                 |               | 1         | 1           |
| Anxiety                                               |                         | 2         |               |                 |               | 2         | 4           |
| Anxiety disorder                                      | 1                       |           |               |                 |               |           | 1           |
| Behaviour disorder                                    |                         | 1         |               |                 |               |           | 1           |
| Bipolar disorder                                      |                         | 4         |               |                 |               |           | 4           |
| Bipolar I disorder                                    |                         | 2         |               |                 |               |           | 2           |
| Completed suicide                                     | 1                       | 2         |               |                 |               |           | 3           |
| Confusional state                                     | 1                       |           |               |                 |               |           | 1           |
| Delirium                                              |                         |           |               |                 |               | 1         | 1           |
| Depression                                            | 2                       | 12        |               |                 |               | 1         | 15          |
| Depression suicidal                                   | 1                       | 1         |               |                 |               | 1         | 3           |
| Drug abuse                                            |                         | 1         |               |                 |               |           | 1           |
| Drug dependence                                       |                         |           |               |                 |               | 1         | 1           |
| Histrionic personality disorder                       |                         | 1         |               |                 |               |           | 1           |
| Immunisation anxiety related reaction                 | 1                       |           |               |                 |               |           | 1           |
| Intentional self-injury                               | 1                       | 1         |               |                 |               |           | 2           |
| Major depression                                      | 4                       | 3         |               |                 |               | 1         | 8           |
| Mania                                                 |                         | 1         |               |                 |               | 1         | 2           |
| Mental status changes                                 |                         | 3         |               |                 |               | 1         | 4           |
| Panic attack                                          |                         | 1         |               |                 |               |           | 1           |

| Event Counts                                                  |                         |            |               |                 |               |           |             |
|---------------------------------------------------------------|-------------------------|------------|---------------|-----------------|---------------|-----------|-------------|
| SOC - PT                                                      | mRNA-1273 vs<br>Placebo | mRNA-1273  | mRNA-1273.211 | mRNA-1273.617.2 | mRNA-1273.213 | Placebo   | Grand Total |
| Schizoaffective disorder                                      | 2                       |            |               |                 |               |           | 2           |
| Schizophrenia                                                 | 1                       |            |               |                 |               |           | 1           |
| Substance use disorder                                        |                         | 3          |               |                 |               |           | 3           |
| Substance-induced mood disorder                               |                         | 1          |               |                 |               |           | 1           |
| Substance-induced psychotic disorder                          | 1                       |            |               |                 |               |           | 1           |
| Suicidal ideation                                             | 5                       | 11         |               |                 |               |           | 16          |
| Suicide attempt                                               | 4                       | 2          |               |                 |               |           | 6           |
| <b>Renal and urinary disorders</b>                            | <b>9</b>                | <b>75</b>  |               | <b>1</b>        |               | <b>9</b>  | <b>94</b>   |
| Acute kidney injury                                           | 3                       | 24         |               | 1               |               | 4         | 32          |
| Bladder prolapse                                              |                         | 2          |               |                 |               |           | 2           |
| Chronic kidney disease                                        | 1                       | 1          |               |                 |               | 1         | 3           |
| Haematuria                                                    |                         | 4          |               |                 |               |           | 4           |
| Hydronephrosis                                                |                         | 4          |               |                 |               |           | 4           |
| Nephritis                                                     |                         | 1          |               |                 |               |           | 1           |
| Nephrolithiasis                                               | 4                       | 18         |               |                 |               | 2         | 24          |
| Obstructive nephropathy                                       | 1                       |            |               |                 |               |           | 1           |
| Renal artery stenosis                                         |                         | 1          |               |                 |               |           | 1           |
| Renal cyst                                                    |                         | 1          |               |                 |               |           | 1           |
| Renal failure                                                 |                         | 6          |               |                 |               |           | 6           |
| Renal impairment                                              |                         |            |               |                 |               | 1         | 1           |
| Ureteric stenosis                                             |                         | 1          |               |                 |               |           | 1           |
| Ureterolithiasis                                              |                         | 3          |               |                 |               |           | 3           |
| Urinary retention                                             |                         | 7          |               |                 |               | 1         | 8           |
| Urinary tract obstruction                                     |                         | 1          |               |                 |               |           | 1           |
| Urogenital fistula                                            |                         | 1          |               |                 |               |           | 1           |
| <b>Reproductive system and breast disorders</b>               | <b>2</b>                | <b>27</b>  |               |                 |               | <b>5</b>  | <b>34</b>   |
| Abnormal uterine bleeding                                     |                         | 1          |               |                 |               |           | 1           |
| Adenomyosis                                                   |                         | 1          |               |                 |               |           | 1           |
| Benign prostatic hyperplasia                                  |                         | 6          |               |                 |               | 1         | 7           |
| Cervical dysplasia                                            |                         | 2          |               |                 |               | 1         | 3           |
| Cervix haemorrhage uterine                                    |                         | 1          |               |                 |               |           | 1           |
| Endometriosis                                                 |                         | 1          |               |                 |               |           | 1           |
| Erectile dysfunction                                          |                         | 1          |               |                 |               |           | 1           |
| Heavy menstrual bleeding                                      |                         | 3          |               |                 |               |           | 3           |
| Menometrorrhagia                                              |                         | 1          |               |                 |               |           | 1           |
| Ovarian cyst                                                  |                         | 2          |               |                 |               | 1         | 3           |
| Ovarian cyst torsion                                          |                         | 1          |               |                 |               |           | 1           |
| Pelvic organ prolapse                                         | 1                       | 1          |               |                 |               |           | 2           |
| Pelvic pain                                                   |                         | 2          |               |                 |               |           | 2           |
| Prostatomegaly                                                |                         | 1          |               |                 |               | 1         | 2           |
| Uterine haemorrhage                                           | 1                       | 2          |               |                 |               |           | 3           |
| Uterine prolapse                                              |                         | 1          |               |                 |               | 1         | 2           |
| <b>Respiratory, thoracic and mediastinal disorders</b>        | <b>27</b>               | <b>117</b> | <b>1</b>      | <b>2</b>        |               | <b>33</b> | <b>180</b>  |
| Acute pulmonary oedema                                        |                         | 1          |               |                 |               |           | 1           |
| Acute respiratory distress syndrome                           | 1                       |            |               |                 |               |           | 1           |
| Acute respiratory failure                                     | 9                       | 12         |               | 1               |               | 6         | 28          |
| Asthma                                                        |                         | 6          |               |                 |               | 1         | 7           |
| Asthma-chronic obstructive pulmonary disease overlap syndrome |                         | 1          |               |                 |               |           | 1           |
| Atelectasis                                                   | 1                       | 1          |               |                 |               |           | 2           |

| Event Counts                                  |                         |           |               |                 |               |          |             |
|-----------------------------------------------|-------------------------|-----------|---------------|-----------------|---------------|----------|-------------|
| SOC - PT                                      | mRNA-1273 vs<br>Placebo | mRNA-1273 | mRNA-1273.211 | mRNA-1273.617.2 | mRNA-1273.213 | Placebo  | Grand Total |
| Bronchial hyperreactivity                     | 1                       |           |               |                 |               |          | 1           |
| Bronchiectasis                                |                         | 1         |               |                 |               |          | 1           |
| Chronic obstructive pulmonary disease         | 3                       | 16        |               |                 |               | 7        | 26          |
| Cough                                         |                         | 1         |               |                 |               |          | 1           |
| Dyspnoea                                      | 1                       | 10        |               | 1               |               |          | 12          |
| Dyspnoea exertional                           |                         | 4         |               |                 |               | 1        | 5           |
| Emphysema                                     | 1                       |           |               |                 |               | 1        | 2           |
| Epistaxis                                     |                         |           |               |                 |               | 1        | 1           |
| Haemothorax                                   |                         | 2         |               |                 |               |          | 2           |
| Hypoxia                                       | 1                       | 1         | 1             |                 |               | 2        | 5           |
| Interstitial lung disease                     |                         |           |               |                 |               | 1        | 1           |
| Laryngeal oedema                              | 1                       |           |               |                 |               |          | 1           |
| Organising pneumonia                          |                         |           |               |                 |               | 1        | 1           |
| Pleural effusion                              |                         | 10        |               |                 |               | 2        | 12          |
| Pleuritic pain                                | 1                       |           |               |                 |               |          | 1           |
| Pneumothorax                                  |                         | 6         |               |                 |               | 2        | 8           |
| Pneumothorax spontaneous                      |                         | 1         |               |                 |               |          | 1           |
| Pulmonary artery thrombosis                   |                         | 1         |               |                 |               |          | 1           |
| Pulmonary embolism                            | 5                       | 27        |               |                 |               | 5        | 37          |
| Pulmonary fibrosis                            |                         |           |               |                 |               | 1        | 1           |
| Pulmonary infarction                          |                         |           |               |                 |               | 1        | 1           |
| Pulmonary mass                                |                         | 1         |               |                 |               |          | 1           |
| Pulmonary oedema                              |                         | 5         |               |                 |               |          | 5           |
| Respiratory acidosis                          |                         | 1         |               |                 |               |          | 1           |
| Respiratory distress                          | 1                       |           |               |                 |               |          | 1           |
| Respiratory failure                           | 1                       | 6         |               |                 |               | 1        | 8           |
| Respiratory tract congestion                  |                         | 1         |               |                 |               |          | 1           |
| Tonsillar hypertrophy                         |                         | 1         |               |                 |               |          | 1           |
| Wheezing                                      |                         | 1         |               |                 |               |          | 1           |
| <b>Skin and subcutaneous tissue disorders</b> |                         | <b>7</b>  |               |                 |               | <b>2</b> | <b>9</b>    |
| Angioedema                                    |                         | 1         |               |                 |               | 1        | 2           |
| Decubitus ulcer                               |                         | 1         |               |                 |               |          | 1           |
| Dermatitis bullous                            |                         |           |               |                 |               | 1        | 1           |
| Drug eruption                                 |                         | 1         |               |                 |               |          | 1           |
| Erythema nodosum                              |                         | 1         |               |                 |               |          | 1           |
| Rash                                          |                         | 1         |               |                 |               |          | 1           |
| Rash vesicular                                |                         | 1         |               |                 |               |          | 1           |
| Urticaria                                     |                         | 1         |               |                 |               |          | 1           |
| <b>Social circumstances</b>                   |                         | <b>1</b>  |               |                 |               | <b>1</b> | <b>2</b>    |
| Physical assault                              |                         | 1         |               |                 |               |          | 1           |
| Sexual abuse                                  |                         |           |               |                 |               | 1        | 1           |
| <b>Surgical and medical procedures</b>        |                         | <b>8</b>  |               |                 |               | <b>1</b> | <b>9</b>    |
| Abdominoplasty                                |                         | 1         |               |                 |               |          | 1           |
| Abortion induced                              |                         | 1         |               |                 |               |          | 1           |
| Knee arthroplasty                             |                         | 2         |               |                 |               |          | 2           |
| Liposuction                                   |                         | 1         |               |                 |               |          | 1           |
| Mammoplasty                                   |                         | 1         |               |                 |               |          | 1           |
| Renal transplant                              |                         | 1         |               |                 |               |          | 1           |
| Revascularisation procedure                   |                         |           |               |                 |               | 1        | 1           |



| Event Counts                          |                         |             |               |                 |               |            |             |
|---------------------------------------|-------------------------|-------------|---------------|-----------------|---------------|------------|-------------|
| SOC - PT                              | mRNA-1273 vs<br>Placebo | mRNA-1273   | mRNA-1273.211 | mRNA-1273.617.2 | mRNA-1273.213 | Placebo    | Grand Total |
| Spinal laminectomy                    |                         | 1           |               |                 |               |            | 1           |
| <b>Vascular disorders</b>             | <b>7</b>                | <b>67</b>   | <b>1</b>      |                 |               | <b>16</b>  | <b>91</b>   |
| Aortic aneurysm                       |                         | 2           |               |                 |               | 1          | 3           |
| Aortic dissection                     |                         | 1           |               |                 |               |            | 1           |
| Aortic stenosis                       |                         | 4           |               |                 |               | 2          | 6           |
| Arterial haemorrhage                  |                         |             |               |                 |               | 1          | 1           |
| Arterial insufficiency                |                         | 1           |               |                 |               |            | 1           |
| Arteriosclerosis                      |                         | 1           |               |                 |               | 1          | 2           |
| Axillary vein thrombosis              |                         | 1           |               |                 |               |            | 1           |
| Deep vein thrombosis                  | 1                       | 12          |               |                 |               | 1          | 14          |
| Embolism                              |                         | 1           |               |                 |               |            | 1           |
| Embolism venous                       |                         | 1           |               |                 |               |            | 1           |
| Extremity necrosis                    |                         | 1           |               |                 |               |            | 1           |
| Fibromuscular dysplasia               |                         |             |               |                 |               | 1          | 1           |
| Haematoma                             | 1                       | 1           |               |                 |               |            | 2           |
| Hypertension                          | 1                       | 7           |               |                 |               | 2          | 10          |
| Hypertensive crisis                   |                         | 1           |               |                 |               |            | 1           |
| Hypertensive emergency                | 1                       |             |               |                 |               | 1          | 2           |
| Hypertensive urgency                  |                         | 5           |               |                 |               | 1          | 6           |
| Hypotension                           |                         | 8           | 1             |                 |               | 3          | 12          |
| Intermittent claudication             |                         | 1           |               |                 |               |            | 1           |
| Ischaemia                             |                         | 1           |               |                 |               |            | 1           |
| Jugular vein thrombosis               |                         | 1           |               |                 |               |            | 1           |
| Orthostatic hypotension               |                         | 4           |               |                 |               |            | 4           |
| Pelvic venous thrombosis              |                         | 1           |               |                 |               |            | 1           |
| Peripheral arterial occlusive disease |                         | 4           |               |                 |               |            | 4           |
| Peripheral artery aneurysm            | 1                       | 1           |               |                 |               |            | 2           |
| Peripheral artery occlusion           |                         | 1           |               |                 |               | 1          | 2           |
| Peripheral vascular disorder          |                         | 1           |               |                 |               |            | 1           |
| Polyarteritis nodosa                  | 1                       |             |               |                 |               |            | 1           |
| Shock                                 | 1                       | 1           |               |                 |               |            | 2           |
| Shock haemorrhagic                    |                         | 1           |               |                 |               |            | 1           |
| Subclavian vein thrombosis            |                         | 1           |               |                 |               |            | 1           |
| Superficial vein thrombosis           |                         |             |               |                 |               | 1          | 1           |
| Thrombosis                            |                         | 1           |               |                 |               |            | 1           |
| Venous thrombosis limb                |                         | 1           |               |                 |               |            | 1           |
| <b>Grand Total</b>                    | <b>318</b>              | <b>1955</b> | <b>26</b>     | <b>9</b>        | <b>1</b>      | <b>348</b> | <b>2657</b> |

**20.3. Appendix 3 Cumulative and Interval Summary Tabulations of Serious and Non-Serious Adverse Reactions from Post-marketing Data Sources**

**Cumulative and Interval Summary Tabulations of Serious and Non Serious Adverse Reactions from Post-marketing Data Sources (Through 31 Decemeber 2021)**

|                                      |                                        | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|--------------------------------------|----------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|                                      |                                        | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM                             | PT                                     | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
| Blood and lymphatic system disorders | *** SOC TOTAL ***                      | 2722                                                                    | 4017       | 7197        | 15615      | 19632             | 0                                                              | 0          |
|                                      | Abdominal lymphadenopathy              | 1                                                                       | 1          | 0           | 2          | 3                 | 0                                                              | 0          |
|                                      | Abnormal clotting factor               | 0                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|                                      | Acquired Von Willebrand's disease      | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                      | Acquired haemophilia                   | 9                                                                       | 13         | 0           | 0          | 13                | 0                                                              | 0          |
|                                      | Agranulocytosis                        | 3                                                                       | 6          | 0           | 0          | 6                 | 0                                                              | 0          |
|                                      | Anaemia                                | 113                                                                     | 206        | 68          | 118        | 324               | 0                                                              | 0          |
|                                      | Anaemia folate deficiency              | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                                      | Anaemia macrocytic                     | 6                                                                       | 9          | 2           | 2          | 11                | 0                                                              | 0          |
|                                      | Anaemia megaloblastic                  | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                      | Anaemia of chronic disease             | 4                                                                       | 6          | 0           | 0          | 6                 | 0                                                              | 0          |
|                                      | Anaemia of pregnancy                   | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|                                      | Anaemia vitamin B12 deficiency         | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|                                      | Anisocytosis                           | 2                                                                       | 5          | 1           | 2          | 7                 | 0                                                              | 0          |
|                                      | Antiphospholipid syndrome              | 15                                                                      | 19         | 0           | 0          | 19                | 0                                                              | 0          |
|                                      | Aplasia pure red cell                  | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                                      | Aplastic anaemia                       | 10                                                                      | 15         | 0           | 0          | 15                | 0                                                              | 0          |
|                                      | Atypical haemolytic uraemic syndrome   | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                                      | Autoimmune haemolytic anaemia          | 14                                                                      | 36         | 0           | 0          | 36                | 0                                                              | 0          |
|                                      | Autoimmune neutropenia                 | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                      | Autoimmune pancytopenia                | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                      | Bandaemia                              | 3                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|                                      | Bicytopenia                            | 3                                                                       | 6          | 0           | 0          | 6                 | 0                                                              | 0          |
|                                      | Blood disorder                         | 12                                                                      | 14         | 8           | 15         | 29                | 0                                                              | 0          |
|                                      | Blood loss anaemia                     | 13                                                                      | 18         | 0           | 0          | 18                | 0                                                              | 0          |
|                                      | Bone marrow disorder                   | 3                                                                       | 3          | 1           | 2          | 5                 | 0                                                              | 0          |
|                                      | Bone marrow failure                    | 3                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|                                      | Bone marrow oedema                     | 2                                                                       | 2          | 1           | 4          | 6                 | 0                                                              | 0          |
|                                      | Bone marrow oedema syndrome            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                      | Bone marrow reticulin fibrosis         | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                      | Breakthrough haemolysis                | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                      | Coagulopathy                           | 31                                                                      | 43         | 16          | 31         | 74                | 0                                                              | 0          |
|                                      | Cold type haemolytic anaemia           | 2                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|                                      | Coombs negative haemolytic anaemia     | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                      | Coombs positive haemolytic anaemia     | 3                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|                                      | Cytopenia                              | 2                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|                                      | Disseminated intravascular coagulation | 19                                                                      | 32         | 0           | 0          | 32                | 0                                                              | 0          |
|                                      | Eosinopenia                            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                      | Eosinophilia                           | 17                                                                      | 24         | 6           | 15         | 39                | 0                                                              | 0          |
|                                      | Erythropoiesis abnormal                | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                      | Evans syndrome                         | 3                                                                       | 6          | 0           | 0          | 6                 | 0                                                              | 0          |
|                                      | Factor VIII inhibition                 | 1                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|                                      | Factor XIII Inhibition                 | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|                                      | Febrile neutropenia                    | 4                                                                       | 11         | 0           | 0          | 11                | 0                                                              | 0          |
|                                      | Granulocytopenia                       | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                      | Granulomatous lymphadenitis            | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |

|          |                                  | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|----------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                  | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                               | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Haemoconcentration               | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Haemolysis                       | 12                                                                      | 24         | 1           | 1          | 25                | 0                                                              | 0          |
|          | Haemolytic anaemia               | 13                                                                      | 26         | 1           | 1          | 27                | 0                                                              | 0          |
|          | Haemolytic uraemic syndrome      | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Haemorrhagic diathesis           | 8                                                                       | 14         | 0           | 0          | 14                | 0                                                              | 0          |
|          | Haemorrhagic disorder            | 3                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Heparin-induced thrombocytopenia | 5                                                                       | 9          | 0           | 0          | 9                 | 0                                                              | 0          |
|          | Hilar lymphadenopathy            | 6                                                                       | 12         | 2           | 3          | 15                | 0                                                              | 0          |
|          | Hyperchromic anaemia             | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Hypercoagulation                 | 9                                                                       | 14         | 4           | 8          | 22                | 0                                                              | 0          |
|          | Hypereosinophilic syndrome       | 1                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Hyperfibrinogenaemia             | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Hyperfibrinolysis                | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Hypergammaglobulinaemia          | 0                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Hyperleukocytosis                | 5                                                                       | 5          | 1           | 1          | 6                 | 0                                                              | 0          |
|          | Hypochromic anaemia              | 2                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Hypofibrinogenaemia              | 0                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Hyposplenism                     | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Immune thrombocytopenia          | 108                                                                     | 244        | 3           | 6          | 250               | 0                                                              | 0          |
|          | Increased tendency to bruise     | 10                                                                      | 18         | 25          | 35         | 53                | 0                                                              | 0          |
|          | Iron deficiency anaemia          | 9                                                                       | 15         | 1           | 5          | 20                | 0                                                              | 0          |
|          | Leukocytosis                     | 72                                                                      | 118        | 13          | 28         | 146               | 0                                                              | 0          |
|          | Leukopenia                       | 44                                                                      | 61         | 3           | 4          | 65                | 0                                                              | 0          |
|          | Lymph node calcification         | 2                                                                       | 2          | 1           | 1          | 3                 | 0                                                              | 0          |
|          | Lymph node haemorrhage           | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Lymph node pain                  | 182                                                                     | 212        | 506         | 1759       | 1971              | 0                                                              | 0          |
|          | Lymph node rupture               | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Lymph node ulcer                 | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Lymphadenitis                    | 43                                                                      | 54         | 157         | 254        | 308               | 0                                                              | 0          |
|          | Lymphadenopathy                  | 1342                                                                    | 1671       | 6317        | 13175      | 14846             | 0                                                              | 0          |
|          | Lymphadenopathy mediastinal      | 13                                                                      | 30         | 1           | 4          | 34                | 0                                                              | 0          |
|          | Lymphatic disorder               | 2                                                                       | 2          | 2           | 7          | 9                 | 0                                                              | 0          |
|          | Lymphocytic infiltration         | 3                                                                       | 3          | 1           | 2          | 5                 | 0                                                              | 0          |
|          | Lymphocytosis                    | 2                                                                       | 5          | 1           | 1          | 6                 | 0                                                              | 0          |
|          | Lymphoid tissue hyperplasia      | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Lymphopenia                      | 11                                                                      | 24         | 4           | 9          | 33                | 0                                                              | 0          |
|          | Macrocytosis                     | 3                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Mast cell activation syndrome    | 11                                                                      | 13         | 2           | 2          | 15                | 0                                                              | 0          |
|          | Mastocytosis                     | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Microcytic anaemia               | 4                                                                       | 5          | 0           | 2          | 7                 | 0                                                              | 0          |
|          | Monoclonal B-cell lymphocytosis  | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Monocytosis                      | 0                                                                       | 3          | 0           | 1          | 4                 | 0                                                              | 0          |
|          | Myelosuppression                 | 0                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Necrotic lymphadenopathy         | 1                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Neutropenia                      | 20                                                                      | 44         | 0           | 1          | 45                | 0                                                              | 0          |
|          | Neutropenia neonatal             | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Neutrophilia                     | 5                                                                       | 6          | 1           | 2          | 8                 | 0                                                              | 0          |
|          | Normochromic anaemia             | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Normochromic normocytic anaemia  | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |

|                   |                                         | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|-------------------|-----------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|                   |                                         | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM          | PT                                      | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|                   | Normocytic anaemia                      | 6                                                                       | 12         | 1           | 2          | 14                | 0                                                              | 0          |
|                   | Nucleated red cells                     | 7                                                                       | 10         | 0           | 0          | 10                | 0                                                              | 0          |
|                   | Pancytopenia                            | 25                                                                      | 53         | 0           | 0          | 53                | 0                                                              | 0          |
|                   | Paratracheal lymphadenopathy            | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|                   | Pernicious anaemia                      | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|                   | Placental transfusion syndrome          | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                   | Platelet disorder                       | 2                                                                       | 5          | 3           | 8          | 13                | 0                                                              | 0          |
|                   | Polychromasia                           | 3                                                                       | 5          | 0           | 1          | 6                 | 0                                                              | 0          |
|                   | Polycythaemia                           | 3                                                                       | 5          | 1           | 4          | 9                 | 0                                                              | 0          |
|                   | Pseudolymphoma                          | 2                                                                       | 2          | 3           | 4          | 6                 | 0                                                              | 0          |
|                   | Red blood cell abnormality              | 1                                                                       | 1          | 1           | 11         | 12                | 0                                                              | 0          |
|                   | Retroperitoneal lymphadenopathy         | 2                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|                   | Rouleaux formation                      | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                   | Schistocytosis                          | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                   | Sickle cell anaemia with crisis         | 5                                                                       | 11         | 0           | 0          | 11                | 0                                                              | 0          |
|                   | Spleen disorder                         | 0                                                                       | 0          | 3           | 5          | 5                 | 0                                                              | 0          |
|                   | Spleen ischaemia                        | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                   | Splenic artery stenosis                 | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                   | Splenic artery thrombosis               | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                   | Splenic calcification                   | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|                   | Splenic cyst                            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                   | Splenic granuloma                       | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                   | Splenic haematoma                       | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                   | Splenic haemorrhage                     | 0                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|                   | Splenic infarction                      | 15                                                                      | 27         | 0           | 0          | 27                | 0                                                              | 0          |
|                   | Splenic lesion                          | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                   | Splenic thrombosis                      | 4                                                                       | 7          | 0           | 0          | 7                 | 0                                                              | 0          |
|                   | Splenic vein thrombosis                 | 1                                                                       | 9          | 0           | 0          | 9                 | 0                                                              | 0          |
|                   | Splenomegaly                            | 18                                                                      | 26         | 7           | 19         | 45                | 0                                                              | 0          |
|                   | Spontaneous haematoma                   | 5                                                                       | 8          | 6           | 13         | 21                | 0                                                              | 0          |
|                   | Spontaneous haemorrhage                 | 2                                                                       | 8          | 0           | 0          | 8                 | 0                                                              | 0          |
|                   | Subcapsular splenic haematoma           | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                   | Thrombocytopenia                        | 281                                                                     | 527        | 11          | 14         | 541               | 0                                                              | 0          |
|                   | Thrombocytopenic purpura                | 9                                                                       | 12         | 1           | 1          | 13                | 0                                                              | 0          |
|                   | Thrombocytosis                          | 8                                                                       | 11         | 2           | 6          | 17                | 0                                                              | 0          |
|                   | Thrombosis with thrombocytopenia syndro | 14                                                                      | 14         | 0           | 0          | 14                | 0                                                              | 0          |
|                   | Thrombotic microangiopathy              | 3                                                                       | 6          | 0           | 0          | 6                 | 0                                                              | 0          |
|                   | Thrombotic thrombocytopenic purpura     | 19                                                                      | 33         | 0           | 0          | 33                | 0                                                              | 0          |
|                   | Thymus enlargement                      | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                   | Warm type haemolytic anaemia            | 2                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|                   | White blood cell disorder               | 2                                                                       | 8          | 5           | 11         | 19                | 0                                                              | 0          |
| Cardiac disorders | *** SOC TOTAL ***                       | 11623                                                                   | 16724      | 5274        | 10607      | 27331             | 0                                                              | 0          |
|                   | Accelerated idioventricular rhythm      | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|                   | Acute cardiac event                     | 1                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|                   | Acute coronary syndrome                 | 27                                                                      | 47         | 0           | 0          | 47                | 0                                                              | 0          |
|                   | Acute left ventricular failure          | 19                                                                      | 31         | 0           | 0          | 31                | 0                                                              | 0          |
|                   | Acute myocardial infarction             | 233                                                                     | 444        | 0           | 0          | 444               | 0                                                              | 0          |
|                   | Agonal rhythm                           | 0                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|                   | Angina pectoris                         | 274                                                                     | 398        | 50          | 60         | 458               | 0                                                              | 0          |

|          |                                      | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|--------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                      | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                   | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Angina unstable                      | 9                                                                       | 17         | 0           | 0          | 17                | 0                                                              | 0          |
|          | Aortic valve calcification           | 2                                                                       | 6          | 0           | 0          | 6                 | 0                                                              | 0          |
|          | Aortic valve disease                 | 1                                                                       | 2          | 1           | 1          | 3                 | 0                                                              | 0          |
|          | Aortic valve incompetence            | 10                                                                      | 15         | 0           | 0          | 15                | 0                                                              | 0          |
|          | Aortic valve sclerosis               | 3                                                                       | 4          | 0           | 1          | 5                 | 0                                                              | 0          |
|          | Aortic valve stenosis                | 7                                                                       | 9          | 0           | 0          | 9                 | 0                                                              | 0          |
|          | Aortic valve thickening              | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Arrhythmia                           | 609                                                                     | 839        | 126         | 145        | 984               | 0                                                              | 0          |
|          | Arrhythmia supraventricular          | 1                                                                       | 3          | 1           | 1          | 4                 | 0                                                              | 0          |
|          | Arrhythmic storm                     | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Arteriosclerosis coronary artery     | 23                                                                      | 35         | 3           | 6          | 41                | 0                                                              | 0          |
|          | Arteriospasm coronary                | 3                                                                       | 9          | 0           | 0          | 9                 | 0                                                              | 0          |
|          | Arteritis coronary                   | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Atrial enlargement                   | 4                                                                       | 8          | 4           | 4          | 12                | 0                                                              | 0          |
|          | Atrial fibrillation                  | 763                                                                     | 1345       | 62          | 75         | 1420              | 0                                                              | 0          |
|          | Atrial flutter                       | 53                                                                      | 84         | 17          | 47         | 131               | 0                                                              | 0          |
|          | Atrial tachycardia                   | 8                                                                       | 11         | 7           | 13         | 24                | 0                                                              | 0          |
|          | Atrial thrombosis                    | 4                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Atrioventricular block               | 25                                                                      | 50         | 14          | 20         | 70                | 0                                                              | 0          |
|          | Atrioventricular block complete      | 20                                                                      | 33         | 1           | 1          | 34                | 0                                                              | 0          |
|          | Atrioventricular block first degree  | 8                                                                       | 12         | 4           | 6          | 18                | 0                                                              | 0          |
|          | Atrioventricular block second degree | 12                                                                      | 15         | 3           | 5          | 20                | 0                                                              | 0          |
|          | Autoimmune pericarditis              | 0                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Bifascicular block                   | 2                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Bradycardia                          | 200                                                                     | 372        | 12          | 39         | 411               | 0                                                              | 0          |
|          | Bradycardia foetal                   | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Bradycardia neonatal                 | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Brugada syndrome                     | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Bundle branch block                  | 1                                                                       | 3          | 4           | 5          | 8                 | 0                                                              | 0          |
|          | Bundle branch block bilateral        | 0                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Bundle branch block left             | 17                                                                      | 24         | 12          | 17         | 41                | 0                                                              | 0          |
|          | Bundle branch block right            | 20                                                                      | 35         | 12          | 21         | 56                | 0                                                              | 0          |
|          | Cardiac amyloidosis                  | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Cardiac aneurysm                     | 3                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Cardiac arrest                       | 257                                                                     | 557        | 1           | 1          | 558               | 0                                                              | 0          |
|          | Cardiac discomfort                   | 41                                                                      | 51         | 101         | 143        | 194               | 0                                                              | 0          |
|          | Cardiac disorder                     | 98                                                                      | 149        | 87          | 160        | 309               | 0                                                              | 0          |
|          | Cardiac dysfunction                  | 22                                                                      | 28         | 0           | 0          | 28                | 0                                                              | 0          |
|          | Cardiac failure                      | 179                                                                     | 302        | 2           | 2          | 304               | 0                                                              | 0          |
|          | Cardiac failure acute                | 29                                                                      | 64         | 0           | 0          | 64                | 0                                                              | 0          |
|          | Cardiac failure chronic              | 6                                                                       | 13         | 0           | 0          | 13                | 0                                                              | 0          |
|          | Cardiac failure congestive           | 156                                                                     | 271        | 3           | 5          | 276               | 0                                                              | 0          |
|          | Cardiac fibrillation                 | 17                                                                      | 22         | 3           | 3          | 25                | 0                                                              | 0          |
|          | Cardiac flutter                      | 309                                                                     | 452        | 97          | 110        | 562               | 0                                                              | 0          |
|          | Cardiac hypertrophy                  | 5                                                                       | 7          | 0           | 7          | 7                 | 0                                                              | 0          |
|          | Cardiac perfusion defect             | 1                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Cardiac sarcoidosis                  | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Cardiac septal hypertrophy           | 1                                                                       | 2          | 0           | 1          | 3                 | 0                                                              | 0          |
|          | Cardiac steatosis                    | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |

|          |                                    | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                    | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                 | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Cardiac tamponade                  | 21                                                                      | 33         | 0           | 0          | 33                | 0                                                              | 0          |
|          | Cardiac valve disease              | 5                                                                       | 5          | 1           | 1          | 6                 | 0                                                              | 0          |
|          | Cardiac valve thickening           | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Cardiac ventricular disorder       | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Cardiac ventricular thrombosis     | 10                                                                      | 18         | 0           | 0          | 18                | 0                                                              | 0          |
|          | Cardio-respiratory arrest          | 74                                                                      | 176        | 0           | 1          | 177               | 0                                                              | 0          |
|          | Cardio-respiratory distress        | 1                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Cardiogenic shock                  | 41                                                                      | 72         | 0           | 0          | 72                | 0                                                              | 0          |
|          | Cardiomegaly                       | 115                                                                     | 160        | 16          | 30         | 190               | 0                                                              | 0          |
|          | Cardiomyopathy                     | 63                                                                      | 86         | 3           | 3          | 89                | 0                                                              | 0          |
|          | Cardiomyopathy acute               | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Cardiopulmonary failure            | 3                                                                       | 8          | 0           | 0          | 8                 | 0                                                              | 0          |
|          | Cardiorenal syndrome               | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Cardiovascular deconditioning      | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Cardiovascular disorder            | 48                                                                      | 67         | 175         | 199        | 266               | 0                                                              | 0          |
|          | Cardiovascular insufficiency       | 7                                                                       | 9          | 1           | 1          | 10                | 0                                                              | 0          |
|          | Cardiovascular symptom             | 10                                                                      | 12         | 2           | 3          | 15                | 0                                                              | 0          |
|          | Carditis                           | 30                                                                      | 37         | 3           | 3          | 40                | 0                                                              | 0          |
|          | Chordae tendinae rupture           | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Chronic left ventricular failure   | 14                                                                      | 22         | 1           | 1          | 23                | 0                                                              | 0          |
|          | Chronotropic incompetence          | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Conduction disorder                | 0                                                                       | 3          | 1           | 2          | 5                 | 0                                                              | 0          |
|          | Congestive cardiomyopathy          | 24                                                                      | 27         | 2           | 2          | 29                | 0                                                              | 0          |
|          | Cor pulmonale                      | 4                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Cor pulmonale acute                | 3                                                                       | 7          | 0           | 0          | 7                 | 0                                                              | 0          |
|          | Coronary artery aneurysm           | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Coronary artery dilatation         | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Coronary artery disease            | 50                                                                      | 82         | 2           | 8          | 90                | 0                                                              | 0          |
|          | Coronary artery dissection         | 13                                                                      | 23         | 0           | 0          | 23                | 0                                                              | 0          |
|          | Coronary artery embolism           | 0                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Coronary artery occlusion          | 42                                                                      | 78         | 0           | 0          | 78                | 0                                                              | 0          |
|          | Coronary artery stenosis           | 17                                                                      | 29         | 0           | 0          | 29                | 0                                                              | 0          |
|          | Coronary artery thrombosis         | 15                                                                      | 25         | 0           | 0          | 25                | 0                                                              | 0          |
|          | Coronary ostial stenosis           | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Defect conduction intraventricular | 1                                                                       | 2          | 1           | 1          | 3                 | 0                                                              | 0          |
|          | Diabetic cardiomyopathy            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Diastolic dysfunction              | 16                                                                      | 26         | 0           | 2          | 28                | 0                                                              | 0          |
|          | Dressler's syndrome                | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Endocarditis noninfective          | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Eosinophilic myocarditis           | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Extrasystoles                      | 72                                                                      | 91         | 163         | 251        | 342               | 0                                                              | 0          |
|          | Foetal arrhythmia                  | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Foetal heart rate disorder         | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Giant cell myocarditis             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Heart alternation                  | 1                                                                       | 1          | 1           | 4          | 5                 | 0                                                              | 0          |
|          | Heart valve calcification          | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Heart valve incompetence           | 6                                                                       | 10         | 3           | 8          | 18                | 0                                                              | 0          |
|          | Hyperdynamic left ventricle        | 2                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Hypersensitivity myocarditis       | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |

|          |                                           | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|-------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                           | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                        | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Hypertensive cardiomegaly                 | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Hypertensive cardiomyopathy               | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Hypertensive heart disease                | 7                                                                       | 10         | 0           | 0          | 10                | 0                                                              | 0          |
|          | Immune-mediated myocarditis               | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Intracardiac mass                         | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Intracardiac thrombus                     | 31                                                                      | 53         | 0           | 0          | 53                | 0                                                              | 0          |
|          | Ischaemic cardiomyopathy                  | 3                                                                       | 7          | 0           | 0          | 7                 | 0                                                              | 0          |
|          | Left atrial dilatation                    | 9                                                                       | 13         | 0           | 0          | 13                | 0                                                              | 0          |
|          | Left atrial enlargement                   | 9                                                                       | 11         | 6           | 7          | 18                | 0                                                              | 0          |
|          | Left ventricular dilatation               | 8                                                                       | 9          | 0           | 0          | 9                 | 0                                                              | 0          |
|          | Left ventricular dysfunction              | 34                                                                      | 45         | 1           | 1          | 46                | 0                                                              | 0          |
|          | Left ventricular enlargement              | 6                                                                       | 6          | 2           | 2          | 8                 | 0                                                              | 0          |
|          | Left ventricular failure                  | 20                                                                      | 32         | 0           | 0          | 32                | 0                                                              | 0          |
|          | Left ventricular hypertrophy              | 15                                                                      | 30         | 10          | 13         | 43                | 0                                                              | 0          |
|          | Long QT syndrome                          | 0                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Microvascular coronary artery disease     | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Mitral valve calcification                | 3                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Mitral valve disease                      | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Mitral valve incompetence                 | 38                                                                      | 58         | 2           | 3          | 61                | 0                                                              | 0          |
|          | Mitral valve prolapse                     | 4                                                                       | 8          | 2           | 6          | 14                | 0                                                              | 0          |
|          | Mitral valve stenosis                     | 1                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Mitral valve thickening                   | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Myocardial fibrosis                       | 9                                                                       | 13         | 0           | 0          | 13                | 0                                                              | 0          |
|          | Myocardial infarction                     | 403                                                                     | 739        | 6           | 7          | 746               | 0                                                              | 0          |
|          | Myocardial injury                         | 16                                                                      | 26         | 0           | 0          | 26                | 0                                                              | 0          |
|          | Myocardial ischaemia                      | 32                                                                      | 47         | 0           | 0          | 47                | 0                                                              | 0          |
|          | Myocardial necrosis                       | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Myocardial oedema                         | 15                                                                      | 18         | 0           | 0          | 18                | 0                                                              | 0          |
|          | Myocardial rupture                        | 4                                                                       | 7          | 0           | 0          | 7                 | 0                                                              | 0          |
|          | Myocarditis                               | 2246                                                                    | 2622       | 50          | 53         | 2675              | 0                                                              | 0          |
|          | Myxomatous mitral valve degeneration      | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Nodal arrhythmia                          | 2                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Nodal rhythm                              | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Palpitations                              | 1684                                                                    | 2046       | 2350        | 5316       | 7362              | 0                                                              | 0          |
|          | Pericardial cyst                          | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Pericardial disease                       | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Pericardial effusion                      | 193                                                                     | 295        | 6           | 8          | 303               | 0                                                              | 0          |
|          | Pericardial fibrosis                      | 6                                                                       | 9          | 1           | 1          | 10                | 0                                                              | 0          |
|          | Pericardial haemorrhage                   | 6                                                                       | 9          | 0           | 0          | 9                 | 0                                                              | 0          |
|          | Pericardial mass                          | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Pericardial rub                           | 2                                                                       | 3          | 1           | 1          | 4                 | 0                                                              | 0          |
|          | Pericarditis                              | 1024                                                                    | 1299       | 66          | 67         | 1366              | 0                                                              | 0          |
|          | Pericarditis constrictive                 | 1                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Pleuropericarditis                        | 8                                                                       | 12         | 0           | 0          | 12                | 0                                                              | 0          |
|          | Postural orthostatic tachycardia syndrome | 17                                                                      | 26         | 21          | 42         | 68                | 0                                                              | 0          |
|          | Prinzmetal angina                         | 7                                                                       | 7          | 0           | 0          | 7                 | 0                                                              | 0          |
|          | Pulmonary valve disease                   | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Pulmonary valve incompetence              | 3                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Pulmonary valve stenosis                  | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |



|                                            |                                      | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|--------------------------------------------|--------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|                                            |                                      | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM                                   | PT                                   | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|                                            | Pulmonary valve thickening           | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                                            | Pulseless electrical activity        | 25                                                                      | 55         | 0           | 1          | 56                | 0                                                              | 0          |
|                                            | Restrictive cardiomyopathy           | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                                            | Rhythm idioventricular               | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                            | Right atrial dilatation              | 6                                                                       | 6          | 1           | 2          | 8                 | 0                                                              | 0          |
|                                            | Right atrial enlargement             | 1                                                                       | 2          | 2           | 3          | 5                 | 0                                                              | 0          |
|                                            | Right ventricular diastolic collapse | 1                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|                                            | Right ventricular dilatation         | 9                                                                       | 14         | 1           | 2          | 16                | 0                                                              | 0          |
|                                            | Right ventricular dysfunction        | 13                                                                      | 20         | 1           | 1          | 21                | 0                                                              | 0          |
|                                            | Right ventricular enlargement        | 4                                                                       | 7          | 1           | 1          | 8                 | 0                                                              | 0          |
|                                            | Right ventricular failure            | 8                                                                       | 17         | 0           | 0          | 17                | 0                                                              | 0          |
|                                            | Right ventricular hypertrophy        | 2                                                                       | 5          | 0           | 1          | 6                 | 0                                                              | 0          |
|                                            | Sigmoid-shaped ventricular septum    | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                            | Silent myocardial infarction         | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                            | Sinoatrial block                     | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                            | Sinus arrest                         | 4                                                                       | 9          | 0           | 0          | 9                 | 0                                                              | 0          |
|                                            | Sinus arrhythmia                     | 14                                                                      | 19         | 7           | 12         | 31                | 0                                                              | 0          |
|                                            | Sinus bradycardia                    | 14                                                                      | 22         | 15          | 29         | 51                | 0                                                              | 0          |
|                                            | Sinus node dysfunction               | 5                                                                       | 11         | 0           | 0          | 11                | 0                                                              | 0          |
|                                            | Sinus tachycardia                    | 67                                                                      | 113        | 65          | 136        | 249               | 0                                                              | 0          |
|                                            | Stress cardiomyopathy                | 22                                                                      | 37         | 3           | 4          | 41                | 0                                                              | 0          |
|                                            | Supraventricular extrasystoles       | 12                                                                      | 19         | 51          | 73         | 92                | 0                                                              | 0          |
|                                            | Supraventricular tachyarrhythmia     | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                            | Supraventricular tachycardia         | 69                                                                      | 115        | 38          | 94         | 209               | 0                                                              | 0          |
|                                            | Systolic dysfunction                 | 6                                                                       | 11         | 1           | 1          | 12                | 0                                                              | 0          |
|                                            | Tachyarrhythmia                      | 8                                                                       | 16         | 4           | 10         | 26                | 0                                                              | 0          |
|                                            | Tachycardia                          | 965                                                                     | 1314       | 1370        | 2995       | 4309              | 0                                                              | 0          |
|                                            | Tachycardia foetal                   | 2                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|                                            | Tachycardia paroxysmal               | 2                                                                       | 5          | 3           | 4          | 9                 | 0                                                              | 0          |
|                                            | Torsade de pointes                   | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                                            | Tricuspid valve disease              | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                                            | Tricuspid valve incompetence         | 29                                                                      | 41         | 1           | 1          | 42                | 0                                                              | 0          |
|                                            | Tricuspid valve prolapse             | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|                                            | Ventricle rupture                    | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                            | Ventricular arrhythmia               | 5                                                                       | 7          | 0           | 0          | 7                 | 0                                                              | 0          |
|                                            | Ventricular dysfunction              | 4                                                                       | 8          | 0           | 0          | 8                 | 0                                                              | 0          |
|                                            | Ventricular dyskinesia               | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                            | Ventricular dyssynchrony             | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                                            | Ventricular enlargement              | 2                                                                       | 4          | 0           | 1          | 5                 | 0                                                              | 0          |
|                                            | Ventricular extrasystoles            | 60                                                                      | 90         | 175         | 282        | 372               | 0                                                              | 0          |
|                                            | Ventricular failure                  | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                                            | Ventricular fibrillation             | 36                                                                      | 72         | 0           | 0          | 72                | 0                                                              | 0          |
|                                            | Ventricular hypertrophy              | 2                                                                       | 5          | 0           | 2          | 7                 | 0                                                              | 0          |
|                                            | Ventricular hypokinesia              | 34                                                                      | 62         | 0           | 1          | 63                | 0                                                              | 0          |
|                                            | Ventricular tachyarrhythmia          | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                                            | Ventricular tachycardia              | 72                                                                      | 127        | 4           | 4          | 131               | 0                                                              | 0          |
|                                            | Wandering pacemaker                  | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|                                            | Wolff-Parkinson-White syndrome       | 0                                                                       | 2          | 1           | 1          | 3                 | 0                                                              | 0          |
| Congenital, familial and genetic disorders | *** SOC TOTAL ***                    | 112                                                                     | 180        | 23          | 75         | 255               | 0                                                              | 0          |

|          |                                            | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|--------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                            | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                         | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Accessory spleen                           | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Alpha-1 antitrypsin deficiency             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Anencephaly                                | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Angelman's syndrome                        | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Ankyloglossia congenital                   | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Antithrombin III deficiency                | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Aorticopulmonary septal defect             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Aplasia                                    | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Arnold-Chiari malformation                 | 2                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Arteriovenous malformation                 | 1                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Atrial septal defect                       | 8                                                                       | 15         | 1           | 3          | 18                | 0                                                              | 0          |
|          | Bicuspid aortic valve                      | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Birth mark                                 | 0                                                                       | 0          | 3           | 5          | 5                 | 0                                                              | 0          |
|          | Branchial cyst                             | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Bronchogenic cyst                          | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Cardiac malposition                        | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Cardiac septal defect                      | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Cerebellar hypoplasia                      | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Cerebral cavernous malformation            | 2                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Cerebral palsy                             | 1                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Cerebrovascular arteriovenous malformation | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Chronic granulomatous disease              | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Cleft lip                                  | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Cleft palate                               | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Cleft uvula                                | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Coloboma                                   | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Colour blindness                           | 2                                                                       | 2          | 0           | 3          | 5                 | 0                                                              | 0          |
|          | Combined immunodeficiency                  | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Congenital acrochordon                     | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Congenital anomaly                         | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Congenital central nervous system anomaly  | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Congenital diaphragmatic hernia            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Congenital ectodermal dysplasia            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Congenital hydronephrosis                  | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Congenital hypercoagulation                | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Congenital nose malformation               | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Congenital skin disorder                   | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Conjoined twins                            | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Corneal dystrophy                          | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Cryptorchism                               | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Cystic fibrosis                            | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Cytogenetic abnormality                    | 1                                                                       | 2          | 0           | 1          | 3                 | 0                                                              | 0          |
|          | DNMT3A gene mutation                       | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Dermoid cyst                               | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Dysmorphism                                | 0                                                                       | 1          | 1           | 3          | 4                 | 0                                                              | 0          |
|          | Ehlers-Danlos syndrome                     | 2                                                                       | 2          | 1           | 2          | 4                 | 0                                                              | 0          |
|          | Epidermal naevus                           | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Epidermal naevus syndrome                  | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Exomphalos                                 | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |

|          |                                              | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|----------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                              | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                           | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Eyelid ptosis congenital                     | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Facioscapulohumeral muscular dystrophy       | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Factor II mutation                           | 0                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Factor IX deficiency                         | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Factor V Leiden carrier                      | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Factor V Leiden mutation                     | 2                                                                       | 3          | 1           | 2          | 5                 | 0                                                              | 0          |
|          | Factor V deficiency                          | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Factor VII deficiency                        | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Factor VIII deficiency                       | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Fallot's tetralogy                           | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Familial mediterranean fever                 | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Foetal chromosome abnormality                | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Foetal malformation                          | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Fragile X carrier                            | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Gastrointestinal malformation                | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Gastroschisis                                | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Gene mutation                                | 2                                                                       | 2          | 0           | 8          | 10                | 0                                                              | 0          |
|          | Glucose-6-phosphate dehydrogenase deficiency | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|          | Grey matter heterotopia                      | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Haemoglobinopathy                            | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Haemophilia                                  | 1                                                                       | 1          | 1           | 2          | 3                 | 0                                                              | 0          |
|          | Haemorrhagic arteriovenous malformation      | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Heart disease congenital                     | 4                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Hereditary angioedema                        | 0                                                                       | 0          | 3           | 6          | 6                 | 0                                                              | 0          |
|          | Hereditary ataxia                            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Hereditary haemolytic anaemia                | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Hereditary optic atrophy                     | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Heterotaxia                                  | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Hydrocele                                    | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|          | Hyperreflexia                                | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|          | Hypertrophic cardiomyopathy                  | 4                                                                       | 6          | 0           | 0          | 6                 | 0                                                              | 0          |
|          | Hypoplastic left heart syndrome              | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Janus kinase 2 mutation                      | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Kidney duplex                                | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Kidney malformation                          | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Laryngomalacia                               | 1                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Limb malformation                            | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Macrocephaly                                 | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Macroglossia                                 | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Malformation venous                          | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Marcus Gunn syndrome                         | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Marfan's syndrome                            | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Methylenetetrahydrofolate reductase gene     | 2                                                                       | 2          | 1           | 1          | 3                 | 0                                                              | 0          |
|          | Methylmalonic aciduria                       | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Microcephaly                                 | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Multiple congenital abnormalities            | 0                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Muscular dystrophy                           | 1                                                                       | 1          | 2           | 6          | 7                 | 0                                                              | 0          |
|          | Myocardial bridging                          | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Naevus flammeus                              | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |

|                             |                                        | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|-----------------------------|----------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|                             |                                        | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM                    | PT                                     | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|                             | Non-compaction cardiomyopathy          | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                             | Oesophageal atresia                    | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                             | Ornithine transcarbamoylase deficiency | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                             | Patent ductus arteriosus               | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                             | Phimosis                               | 1                                                                       | 1          | 0           | 2          | 3                 | 0                                                              | 0          |
|                             | Porencephaly                           | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                             | Porphyria acute                        | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                             | Protein C deficiency                   | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                             | Protein S deficiency                   | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                             | Renal aplasia                          | 2                                                                       | 2          | 0           | 1          | 3                 | 0                                                              | 0          |
|                             | Renal fusion anomaly                   | 0                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|                             | Right-to-left cardiac shunt            | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                             | Roberts syndrome                       | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|                             | Sickle cell anaemia                    | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                             | Sickle cell disease                    | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|                             | Spine malformation                     | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                             | Stiff skin syndrome                    | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                             | Syringomyelia                          | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                             | Thyroglossal cyst                      | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|                             | Tourette's disorder                    | 0                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                             | Tracheo-oesophageal fistula            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                             | Transposition of the great vessels     | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                             | Trisomy 22                             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                             | Turner's syndrome                      | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                             | Type V hyperlipidaemia                 | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                             | Vascular malformation                  | 1                                                                       | 2          | 0           | 1          | 3                 | 0                                                              | 0          |
|                             | Venous angioma of brain                | 2                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|                             | Ventricular septal defect              | 4                                                                       | 8          | 0           | 0          | 8                 | 0                                                              | 0          |
|                             | Von Willebrand's disease               | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
| Ear and labyrinth disorders | *** SOC TOTAL ***                      | 2128                                                                    | 3680       | 3278        | 9440       | 13120             | 0                                                              | 0          |
|                             | Acute vestibular syndrome              | 1                                                                       | 4          | 1           | 1          | 5                 | 0                                                              | 0          |
|                             | Auditory disorder                      | 3                                                                       | 6          | 11          | 23         | 29                | 0                                                              | 0          |
|                             | Auricular swelling                     | 0                                                                       | 1          | 1           | 2          | 3                 | 0                                                              | 0          |
|                             | Autoimmune inner ear disease           | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|                             | Autophony                              | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|                             | Cerumen impaction                      | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|                             | Conductive deafness                    | 1                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|                             | Deafness                               | 164                                                                     | 461        | 18          | 32         | 493               | 0                                                              | 0          |
|                             | Deafness bilateral                     | 18                                                                      | 41         | 0           | 0          | 41                | 0                                                              | 0          |
|                             | Deafness neurosensory                  | 39                                                                      | 119        | 1           | 3          | 122               | 0                                                              | 0          |
|                             | Deafness permanent                     | 5                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|                             | Deafness transitory                    | 7                                                                       | 16         | 1           | 2          | 18                | 0                                                              | 0          |
|                             | Deafness unilateral                    | 130                                                                     | 388        | 7           | 16         | 404               | 0                                                              | 0          |
|                             | Dysacusis                              | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|                             | Ear canal erythema                     | 1                                                                       | 1          | 0           | 2          | 3                 | 0                                                              | 0          |
|                             | Ear congestion                         | 4                                                                       | 10         | 21          | 72         | 82                | 0                                                              | 0          |
|                             | Ear deformity acquired                 | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|                             | Ear discomfort                         | 72                                                                      | 118        | 218         | 696        | 814               | 0                                                              | 0          |
|                             | Ear disorder                           | 3                                                                       | 6          | 12          | 26         | 32                | 0                                                              | 0          |

|                     |                                        | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|---------------------|----------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|                     |                                        | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM            | PT                                     | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|                     | Ear haemorrhage                        | 1                                                                       | 1          | 8           | 17         | 18                | 0                                                              | 0          |
|                     | Ear inflammation                       | 1                                                                       | 1          | 6           | 6          | 7                 | 0                                                              | 0          |
|                     | Ear pain                               | 243                                                                     | 314        | 456         | 1370       | 1684              | 0                                                              | 0          |
|                     | Ear pruritus                           | 2                                                                       | 4          | 12          | 82         | 86                | 0                                                              | 0          |
|                     | Ear swelling                           | 17                                                                      | 27         | 29          | 151        | 178               | 0                                                              | 0          |
|                     | Endolymphatic hydrops                  | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                     | Eustachian tube disorder               | 0                                                                       | 0          | 3           | 6          | 6                 | 0                                                              | 0          |
|                     | Eustachian tube dysfunction            | 2                                                                       | 2          | 4           | 13         | 15                | 0                                                              | 0          |
|                     | Eustachian tube obstruction            | 1                                                                       | 2          | 2           | 3          | 5                 | 0                                                              | 0          |
|                     | Excessive cerumen production           | 2                                                                       | 2          | 3           | 9          | 11                | 0                                                              | 0          |
|                     | External ear disorder                  | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|                     | External ear inflammation              | 2                                                                       | 2          | 2           | 6          | 8                 | 0                                                              | 0          |
|                     | External ear pain                      | 1                                                                       | 3          | 5           | 16         | 19                | 0                                                              | 0          |
|                     | Haematotympanum                        | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                     | Hyperacusis                            | 29                                                                      | 42         | 55          | 169        | 211               | 0                                                              | 0          |
|                     | Hypoacusis                             | 111                                                                     | 159        | 152         | 385        | 544               | 0                                                              | 0          |
|                     | Inner ear disorder                     | 3                                                                       | 4          | 3           | 14         | 18                | 0                                                              | 0          |
|                     | Inner ear infarction                   | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                     | Inner ear inflammation                 | 2                                                                       | 4          | 5           | 16         | 20                | 0                                                              | 0          |
|                     | Mastoid disorder                       | 2                                                                       | 3          | 2           | 3          | 6                 | 0                                                              | 0          |
|                     | Mastoid effusion                       | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|                     | Meniere's disease                      | 21                                                                      | 45         | 5           | 7          | 52                | 0                                                              | 0          |
|                     | Middle ear disorder                    | 0                                                                       | 1          | 1           | 2          | 3                 | 0                                                              | 0          |
|                     | Middle ear effusion                    | 1                                                                       | 2          | 10          | 32         | 34                | 0                                                              | 0          |
|                     | Middle ear inflammation                | 2                                                                       | 2          | 5           | 7          | 9                 | 0                                                              | 0          |
|                     | Misophonia                             | 1                                                                       | 1          | 1           | 2          | 3                 | 0                                                              | 0          |
|                     | Mixed deafness                         | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                     | Motion sickness                        | 13                                                                      | 19         | 10          | 46         | 65                | 0                                                              | 0          |
|                     | Neurosensory hypoacusis                | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|                     | Noninfective myringitis                | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|                     | Otolithiasis                           | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|                     | Otorrhoea                              | 1                                                                       | 2          | 5           | 16         | 18                | 0                                                              | 0          |
|                     | Paraesthesia ear                       | 1                                                                       | 1          | 3           | 9          | 10                | 0                                                              | 0          |
|                     | Presbycusis                            | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|                     | Red ear syndrome                       | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|                     | Sudden hearing loss                    | 108                                                                     | 186        | 10          | 11         | 197               | 0                                                              | 0          |
|                     | Superior semicircular canal dehiscence | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|                     | Tinnitus                               | 570                                                                     | 872        | 1147        | 3235       | 4107              | 0                                                              | 0          |
|                     | Tympanic membrane disorder             | 1                                                                       | 1          | 3           | 4          | 5                 | 0                                                              | 0          |
|                     | Tympanic membrane hyperaemia           | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|                     | Tympanic membrane perforation          | 1                                                                       | 2          | 0           | 1          | 3                 | 0                                                              | 0          |
|                     | Vertigo                                | 489                                                                     | 721        | 985         | 2792       | 3513              | 0                                                              | 0          |
|                     | Vertigo labyrinthine                   | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|                     | Vertigo positional                     | 24                                                                      | 33         | 42          | 102        | 135               | 0                                                              | 0          |
|                     | Vestibular disorder                    | 19                                                                      | 30         | 6           | 16         | 46                | 0                                                              | 0          |
|                     | Vestibular paroxysmia                  | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
| Endocrine disorders | *** SOC TOTAL ***                      | 295                                                                     | 409        | 169         | 258        | 667               | 0                                                              | 0          |
|                     | Addison's disease                      | 3                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|                     | Adrenal disorder                       | 1                                                                       | 1          | 3           | 9          | 10                | 0                                                              | 0          |

|          |                                              | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|----------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                              | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                           | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Adrenal haemorrhage                          | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Adrenal insufficiency                        | 7                                                                       | 10         | 0           | 0          | 10                | 0                                                              | 0          |
|          | Adrenal mass                                 | 4                                                                       | 9          | 1           | 1          | 10                | 0                                                              | 0          |
|          | Adrenocortical insufficiency acute           | 9                                                                       | 16         | 0           | 0          | 16                | 0                                                              | 0          |
|          | Adrenocorticotrophic hormone deficiency      | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Anovulatory cycle                            | 9                                                                       | 9          | 19          | 22         | 31                | 0                                                              | 0          |
|          | Autoimmune hypothyroidism                    | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Autoimmune thyroid disorder                  | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Autoimmune thyroiditis                       | 32                                                                      | 44         | 4           | 5          | 49                | 0                                                              | 0          |
|          | Basedow's disease                            | 40                                                                      | 47         | 4           | 5          | 52                | 0                                                              | 0          |
|          | Carcinoid syndrome                           | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Cushing's syndrome                           | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Delayed menarche                             | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Diabetes insipidus                           | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Endocrine disorder                           | 1                                                                       | 1          | 1           | 2          | 3                 | 0                                                              | 0          |
|          | Goitre                                       | 10                                                                      | 12         | 25          | 41         | 53                | 0                                                              | 0          |
|          | Growth hormone deficiency                    | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Hyperadrenalism                              | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Hyperaldosteronism                           | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Hyperparathyroidism                          | 0                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Hyperparathyroidism secondary                | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Hyperprolactinaemia                          | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Hyperthyroidism                              | 54                                                                      | 77         | 11          | 12         | 89                | 0                                                              | 0          |
|          | Hypogonadism                                 | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Hypophysitis                                 | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Hypopituitarism                              | 3                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Hypothalamo-pituitary disorder               | 4                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Hypothyroidism                               | 44                                                                      | 60         | 3           | 10         | 70                | 0                                                              | 0          |
|          | Immune-mediated hyperthyroidism              | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Inappropriate antidiuretic hormone secretion | 5                                                                       | 11         | 0           | 0          | 11                | 0                                                              | 0          |
|          | Myxoedema                                    | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Ovulation delayed                            | 4                                                                       | 5          | 12          | 15         | 20                | 0                                                              | 0          |
|          | Parathyroid disorder                         | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Parathyroid gland enlargement                | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Pituitary haemorrhage                        | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Pituitary-dependent Cushing's syndrome       | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Polyglandular disorder                       | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Premature menarche                           | 0                                                                       | 0          | 2           | 3          | 3                 | 0                                                              | 0          |
|          | Primary hyperaldosteronism                   | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Secondary adrenocortical insufficiency       | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Secondary hypogonadism                       | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Secondary hypothyroidism                     | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Silent thyroiditis                           | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Steroid withdrawal syndrome                  | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Testicular failure                           | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Thyroid atrophy                              | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Thyroid calcification                        | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|          | Thyroid cyst                                 | 4                                                                       | 5          | 2           | 3          | 8                 | 0                                                              | 0          |
|          | Thyroid disorder                             | 2                                                                       | 6          | 20          | 31         | 37                | 0                                                              | 0          |

|               |                                  | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|---------------|----------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|               |                                  | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM      | PT                               | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|               | Thyroid mass                     | 9                                                                       | 10         | 6           | 14         | 24                | 0                                                              | 0          |
|               | Thyroid pain                     | 1                                                                       | 1          | 7           | 11         | 12                | 0                                                              | 0          |
|               | Thyroiditis                      | 10                                                                      | 13         | 17          | 32         | 45                | 0                                                              | 0          |
|               | Thyroiditis acute                | 5                                                                       | 6          | 0           | 0          | 6                 | 0                                                              | 0          |
|               | Thyroiditis subacute             | 12                                                                      | 17         | 25          | 31         | 48                | 0                                                              | 0          |
|               | Thyrotoxic crisis                | 2                                                                       | 4          | 1           | 1          | 5                 | 0                                                              | 0          |
| Eye disorders | *** SOC TOTAL ***                | 2911                                                                    | 4704       | 4023        | 12248      | 16952             | 0                                                              | 0          |
|               | Abnormal sensation in eye        | 4                                                                       | 8          | 23          | 74         | 82                | 0                                                              | 0          |
|               | Accommodation disorder           | 3                                                                       | 3          | 5           | 7          | 10                | 0                                                              | 0          |
|               | Acute macular neuroretinopathy   | 2                                                                       | 2          | 1           | 1          | 3                 | 0                                                              | 0          |
|               | Age-related macular degeneration | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|               | Allergic keratitis               | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|               | Altered visual depth perception  | 2                                                                       | 5          | 1           | 9          | 14                | 0                                                              | 0          |
|               | Amaurosis                        | 2                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|               | Amaurosis fugax                  | 8                                                                       | 14         | 0           | 1          | 15                | 0                                                              | 0          |
|               | Amblyopia                        | 2                                                                       | 4          | 1           | 5          | 9                 | 0                                                              | 0          |
|               | Angle closure glaucoma           | 0                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|               | Anterior chamber inflammation    | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|               | Asthenopia                       | 20                                                                      | 25         | 47          | 160        | 185               | 0                                                              | 0          |
|               | Astigmatism                      | 1                                                                       | 2          | 2           | 2          | 4                 | 0                                                              | 0          |
|               | Autoimmune eye disorder          | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|               | Binocular eye movement disorder  | 1                                                                       | 2          | 2           | 4          | 6                 | 0                                                              | 0          |
|               | Blepharal pigmentation           | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|               | Blepharitis                      | 3                                                                       | 3          | 13          | 36         | 39                | 0                                                              | 0          |
|               | Blepharospasm                    | 24                                                                      | 35         | 83          | 187        | 222               | 0                                                              | 0          |
|               | Blindness                        | 148                                                                     | 346        | 6           | 23         | 369               | 0                                                              | 0          |
|               | Blindness transient              | 23                                                                      | 63         | 6           | 9          | 72                | 0                                                              | 0          |
|               | Blindness unilateral             | 75                                                                      | 154        | 5           | 5          | 159               | 0                                                              | 0          |
|               | Cataract                         | 14                                                                      | 30         | 1           | 3          | 33                | 0                                                              | 0          |
|               | Central vision loss              | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|               | Chalazion                        | 0                                                                       | 0          | 6           | 13         | 13                | 0                                                              | 0          |
|               | Chloropsia                       | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|               | Chorioretinal atrophy            | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|               | Chorioretinal disorder           | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|               | Chorioretinopathy                | 9                                                                       | 10         | 0           | 0          | 10                | 0                                                              | 0          |
|               | Chromatopsia                     | 0                                                                       | 0          | 3           | 12         | 12                | 0                                                              | 0          |
|               | Cogan's syndrome                 | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|               | Colour blindness acquired        | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|               | Conjunctival cyst                | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|               | Conjunctival disorder            | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|               | Conjunctival haemorrhage         | 32                                                                      | 81         | 7           | 15         | 96                | 0                                                              | 0          |
|               | Conjunctival hyperaemia          | 5                                                                       | 9          | 10          | 17         | 26                | 0                                                              | 0          |
|               | Conjunctival oedema              | 1                                                                       | 2          | 1           | 3          | 5                 | 0                                                              | 0          |
|               | Conjunctivitis allergic          | 1                                                                       | 2          | 4           | 6          | 8                 | 0                                                              | 0          |
|               | Corneal defect                   | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|               | Corneal disorder                 | 2                                                                       | 2          | 1           | 3          | 5                 | 0                                                              | 0          |
|               | Corneal endotheliitis            | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|               | Corneal irritation               | 0                                                                       | 0          | 1           | 3          | 3                 | 0                                                              | 0          |
|               | Corneal lesion                   | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |

|          |                                           | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|-------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                           | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                        | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Corneal oedema                            | 1                                                                       | 1          | 2           | 5          | 6                 | 0                                                              | 0          |
|          | Corneal opacity                           | 3                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Cyanopsia                                 | 0                                                                       | 1          | 0           | 2          | 3                 | 0                                                              | 0          |
|          | Cystoid macular oedema                    | 3                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Dacryostenosis acquired                   | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|          | Dark circles under eyes                   | 1                                                                       | 2          | 3           | 19         | 21                | 0                                                              | 0          |
|          | Deposit eye                               | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Dermatochalasis                           | 0                                                                       | 0          | 0           | 10         | 10                | 0                                                              | 0          |
|          | Detachment of macular retinal pigment epi | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Diabetic retinopathy                      | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Diplopia                                  | 119                                                                     | 205        | 110         | 278        | 483               | 0                                                              | 0          |
|          | Dry eye                                   | 37                                                                      | 46         | 81          | 193        | 239               | 0                                                              | 0          |
|          | Dyschromatopsia                           | 6                                                                       | 8          | 2           | 13         | 21                | 0                                                              | 0          |
|          | Eczema eyelids                            | 0                                                                       | 0          | 4           | 6          | 6                 | 0                                                              | 0          |
|          | Endocrine ophthalmopathy                  | 5                                                                       | 6          | 1           | 1          | 7                 | 0                                                              | 0          |
|          | Entropion                                 | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Epi-retinal membrane                      | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Episcleritis                              | 1                                                                       | 3          | 1           | 10         | 13                | 0                                                              | 0          |
|          | Erythema of eyelid                        | 1                                                                       | 1          | 13          | 51         | 52                | 0                                                              | 0          |
|          | Erythroptosis                             | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|          | Excessive eye blinking                    | 2                                                                       | 3          | 3           | 12         | 15                | 0                                                              | 0          |
|          | Exophthalmos                              | 11                                                                      | 19         | 0           | 0          | 19                | 0                                                              | 0          |
|          | Extraocular muscle disorder               | 1                                                                       | 1          | 2           | 2          | 3                 | 0                                                              | 0          |
|          | Extraocular muscle paresis                | 7                                                                       | 21         | 0           | 0          | 21                | 0                                                              | 0          |
|          | Exudative retinopathy                     | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Eye allergy                               | 2                                                                       | 3          | 5           | 11         | 14                | 0                                                              | 0          |
|          | Eye colour change                         | 1                                                                       | 2          | 9           | 25         | 27                | 0                                                              | 0          |
|          | Eye discharge                             | 8                                                                       | 9          | 18          | 60         | 69                | 0                                                              | 0          |
|          | Eye disorder                              | 30                                                                      | 37         | 50          | 138        | 175               | 0                                                              | 0          |
|          | Eye haematoma                             | 2                                                                       | 5          | 2           | 2          | 7                 | 0                                                              | 0          |
|          | Eye haemorrhage                           | 51                                                                      | 135        | 10          | 19         | 154               | 0                                                              | 0          |
|          | Eye infarction                            | 5                                                                       | 9          | 0           | 0          | 9                 | 0                                                              | 0          |
|          | Eye inflammation                          | 9                                                                       | 13         | 44          | 80         | 93                | 0                                                              | 0          |
|          | Eye irritation                            | 30                                                                      | 45         | 128         | 454        | 499               | 0                                                              | 0          |
|          | Eye movement disorder                     | 28                                                                      | 51         | 42          | 205        | 256               | 0                                                              | 0          |
|          | Eye muscle entrapment                     | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Eye oedema                                | 7                                                                       | 9          | 12          | 24         | 33                | 0                                                              | 0          |
|          | Eye opacity                               | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Eye pain                                  | 292                                                                     | 375        | 483         | 1246       | 1621              | 0                                                              | 0          |
|          | Eye paraesthesia                          | 4                                                                       | 4          | 3           | 4          | 8                 | 0                                                              | 0          |
|          | Eye pruritus                              | 27                                                                      | 43         | 135         | 532        | 575               | 0                                                              | 0          |
|          | Eye swelling                              | 91                                                                      | 132        | 245         | 1022       | 1154              | 0                                                              | 0          |
|          | Eye symptom                               | 0                                                                       | 0          | 0           | 6          | 6                 | 0                                                              | 0          |
|          | Eye ulcer                                 | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|          | Eyelash discolouration                    | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Eyelid bleeding                           | 0                                                                       | 1          | 1           | 2          | 3                 | 0                                                              | 0          |
|          | Eyelid cyst                               | 1                                                                       | 2          | 0           | 1          | 3                 | 0                                                              | 0          |
|          | Eyelid disorder                           | 6                                                                       | 9          | 7           | 37         | 46                | 0                                                              | 0          |
|          | Eyelid exfoliation                        | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |



|          |                                 | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|---------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                 | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                              | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Eyelid function disorder        | 11                                                                      | 29         | 9           | 46         | 75                | 0                                                              | 0          |
|          | Eyelid haematoma                | 0                                                                       | 0          | 6           | 10         | 10                | 0                                                              | 0          |
|          | Eyelid irritation               | 2                                                                       | 2          | 10          | 29         | 31                | 0                                                              | 0          |
|          | Eyelid margin crusting          | 0                                                                       | 0          | 1           | 22         | 22                | 0                                                              | 0          |
|          | Eyelid myoclonus                | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Eyelid myokymia                 | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Eyelid oedema                   | 21                                                                      | 28         | 48          | 93         | 121               | 0                                                              | 0          |
|          | Eyelid pain                     | 0                                                                       | 1          | 10          | 33         | 34                | 0                                                              | 0          |
|          | Eyelid ptosis                   | 23                                                                      | 41         | 26          | 95         | 136               | 0                                                              | 0          |
|          | Eyelid rash                     | 2                                                                       | 5          | 3           | 20         | 25                | 0                                                              | 0          |
|          | Eyelid retraction               | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Eyelid sensory disorder         | 1                                                                       | 1          | 0           | 11         | 12                | 0                                                              | 0          |
|          | Eyelid skin dryness             | 0                                                                       | 0          | 1           | 6          | 6                 | 0                                                              | 0          |
|          | Eyelid thickening               | 0                                                                       | 1          | 2           | 5          | 6                 | 0                                                              | 0          |
|          | Eyelids pruritus                | 3                                                                       | 4          | 11          | 43         | 47                | 0                                                              | 0          |
|          | Foreign body sensation in eyes  | 5                                                                       | 6          | 5           | 20         | 26                | 0                                                              | 0          |
|          | Gaze palsy                      | 35                                                                      | 94         | 2           | 9          | 103               | 0                                                              | 0          |
|          | Glare                           | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Glaucoma                        | 12                                                                      | 20         | 1           | 2          | 22                | 0                                                              | 0          |
|          | Glaucomatocyclitic crises       | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Growth of eyelashes             | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|          | Halo vision                     | 2                                                                       | 2          | 2           | 6          | 8                 | 0                                                              | 0          |
|          | Heterophoria                    | 0                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Hippus                          | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Holmes-Adie pupil               | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Hyalosis asteroid               | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Hypermetropia                   | 0                                                                       | 0          | 2           | 5          | 5                 | 0                                                              | 0          |
|          | Hypoaesthesia eye               | 6                                                                       | 9          | 11          | 49         | 58                | 0                                                              | 0          |
|          | Idiopathic orbital inflammation | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Iridocyclitis                   | 6                                                                       | 16         | 1           | 2          | 18                | 0                                                              | 0          |
|          | Iris adhesions                  | 1                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Iris discolouration             | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Iritis                          | 9                                                                       | 10         | 9           | 24         | 34                | 0                                                              | 0          |
|          | Keratitis                       | 4                                                                       | 7          | 8           | 10         | 17                | 0                                                              | 0          |
|          | Keratitis interstitial          | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Lacrimonial disorder            | 0                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Lacrimonial haemorrhage         | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Lacrimation decreased           | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|          | Lacrimation disorder            | 1                                                                       | 1          | 3           | 3          | 4                 | 0                                                              | 0          |
|          | Lacrimation increased           | 32                                                                      | 46         | 110         | 475        | 521               | 0                                                              | 0          |
|          | Lagophthalmos                   | 3                                                                       | 4          | 4           | 17         | 21                | 0                                                              | 0          |
|          | Lenticular opacities            | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Lid lag                         | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|          | Lid sulcus deepened             | 3                                                                       | 3          | 0           | 4          | 7                 | 0                                                              | 0          |
|          | Limbal swelling                 | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Macular degeneration            | 7                                                                       | 11         | 0           | 1          | 12                | 0                                                              | 0          |
|          | Macular detachment              | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Macular hole                    | 2                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Macular oedema                  | 10                                                                      | 16         | 0           | 0          | 16                | 0                                                              | 0          |

|          |                                          | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                          | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                       | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Macular pseudohole                       | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Macular telangiectasia                   | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Maculopathy                              | 4                                                                       | 4          | 2           | 2          | 6                 | 0                                                              | 0          |
|          | Meibomian gland discharge                | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Meibomian gland dysfunction              | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Metamorphopsia                           | 9                                                                       | 13         | 18          | 48         | 61                | 0                                                              | 0          |
|          | Miosis                                   | 5                                                                       | 7          | 5           | 19         | 26                | 0                                                              | 0          |
|          | Mydriasis                                | 16                                                                      | 22         | 15          | 64         | 86                | 0                                                              | 0          |
|          | Myopia                                   | 2                                                                       | 2          | 3           | 5          | 7                 | 0                                                              | 0          |
|          | Necrotising retinitis                    | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Neovascular age-related macular degenera | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Neurological eyelid disorder             | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Night blindness                          | 1                                                                       | 1          | 2           | 4          | 5                 | 0                                                              | 0          |
|          | Ocular discomfort                        | 27                                                                      | 43         | 165         | 398        | 441               | 0                                                              | 0          |
|          | Ocular hyperaemia                        | 43                                                                      | 62         | 158         | 554        | 616               | 0                                                              | 0          |
|          | Ocular hypertension                      | 9                                                                       | 13         | 2           | 2          | 15                | 0                                                              | 0          |
|          | Ocular ischaemic syndrome                | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Ocular myasthenia                        | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Ocular rosacea                           | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Ocular vascular disorder                 | 2                                                                       | 3          | 0           | 1          | 4                 | 0                                                              | 0          |
|          | Oculogyric crisis                        | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Ophthalmic artery thrombosis             | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Ophthalmic vein thrombosis               | 7                                                                       | 10         | 0           | 0          | 10                | 0                                                              | 0          |
|          | Ophthalmoplegia                          | 14                                                                      | 26         | 1           | 1          | 27                | 0                                                              | 0          |
|          | Optic atrophy                            | 0                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Optic disc hyperaemia                    | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Optic discs blurred                      | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Optic ischaemic neuropathy               | 19                                                                      | 32         | 0           | 0          | 32                | 0                                                              | 0          |
|          | Optic nerve compression                  | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Optic nerve disorder                     | 6                                                                       | 7          | 1           | 4          | 11                | 0                                                              | 0          |
|          | Optic nerve infarction                   | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Optic nerve sheath haemorrhage           | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Optic neuropathy                         | 4                                                                       | 7          | 0           | 0          | 7                 | 0                                                              | 0          |
|          | Orbital haematoma                        | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Orbital myositis                         | 0                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Orbital oedema                           | 0                                                                       | 4          | 2           | 2          | 6                 | 0                                                              | 0          |
|          | Orbital swelling                         | 0                                                                       | 0          | 2           | 5          | 5                 | 0                                                              | 0          |
|          | Oscillopsia                              | 3                                                                       | 3          | 0           | 1          | 4                 | 0                                                              | 0          |
|          | Panophthalmitis                          | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Papilloedema                             | 13                                                                      | 32         | 0           | 0          | 32                | 0                                                              | 0          |
|          | Papillophlebitis                         | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Paralytic lagophthalmos                  | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Parophthalmia                            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Periorbital discomfort                   | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|          | Periorbital inflammation                 | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Periorbital irritation                   | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Periorbital oedema                       | 3                                                                       | 6          | 13          | 58         | 64                | 0                                                              | 0          |
|          | Periorbital pain                         | 1                                                                       | 3          | 1           | 6          | 9                 | 0                                                              | 0          |
|          | Periorbital swelling                     | 21                                                                      | 29         | 50          | 248        | 277               | 0                                                              | 0          |

|          |                                   | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|-----------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                   | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Photophobia                       | 176                                                                     | 214        | 188         | 598        | 812               | 0                                                              | 0          |
|          | Photopsia                         | 36                                                                      | 41         | 50          | 124        | 165               | 0                                                              | 0          |
|          | Pinguecula                        | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Polypoidal choroidal vasculopathy | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Presbyopia                        | 1                                                                       | 1          | 2           | 2          | 3                 | 0                                                              | 0          |
|          | Punctate keratitis                | 3                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Pupil fixed                       | 7                                                                       | 13         | 0           | 1          | 14                | 0                                                              | 0          |
|          | Pupillary disorder                | 0                                                                       | 2          | 2           | 2          | 4                 | 0                                                              | 0          |
|          | Pupillary reflex impaired         | 2                                                                       | 4          | 0           | 1          | 5                 | 0                                                              | 0          |
|          | Pupils unequal                    | 6                                                                       | 7          | 8           | 12         | 19                | 0                                                              | 0          |
|          | Purtscher retinopathy             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Refraction disorder               | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Retinal artery embolism           | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Retinal artery occlusion          | 21                                                                      | 49         | 0           | 0          | 49                | 0                                                              | 0          |
|          | Retinal artery thrombosis         | 2                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Retinal degeneration              | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Retinal deposits                  | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Retinal detachment                | 32                                                                      | 50         | 0           | 0          | 50                | 0                                                              | 0          |
|          | Retinal disorder                  | 4                                                                       | 5          | 3           | 6          | 11                | 0                                                              | 0          |
|          | Retinal exudates                  | 5                                                                       | 6          | 0           | 0          | 6                 | 0                                                              | 0          |
|          | Retinal haemorrhage               | 19                                                                      | 30         | 0           | 0          | 30                | 0                                                              | 0          |
|          | Retinal infarction                | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Retinal ischaemia                 | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Retinal oedema                    | 4                                                                       | 7          | 0           | 0          | 7                 | 0                                                              | 0          |
|          | Retinal scar                      | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Retinal tear                      | 5                                                                       | 11         | 1           | 1          | 12                | 0                                                              | 0          |
|          | Retinal vascular disorder         | 1                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Retinal vascular occlusion        | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Retinal vascular thrombosis       | 6                                                                       | 11         | 1           | 2          | 13                | 0                                                              | 0          |
|          | Retinal vasculitis                | 2                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Retinal vein occlusion            | 46                                                                      | 64         | 1           | 1          | 65                | 0                                                              | 0          |
|          | Retinal vein thrombosis           | 13                                                                      | 20         | 0           | 2          | 22                | 0                                                              | 0          |
|          | Retinopathy                       | 2                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Rhegmatogenous retinal detachment | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Saccadic eye movement             | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Scintillating scotoma             | 6                                                                       | 6          | 6           | 10         | 16                | 0                                                              | 0          |
|          | Scleral discolouration            | 2                                                                       | 2          | 0           | 1          | 3                 | 0                                                              | 0          |
|          | Scleral disorder                  | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Scleral haemorrhage               | 2                                                                       | 4          | 1           | 2          | 6                 | 0                                                              | 0          |
|          | Scleral hyperaemia                | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Scleral oedema                    | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Scleritis                         | 8                                                                       | 17         | 0           | 0          | 17                | 0                                                              | 0          |
|          | Scleritis allergic                | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Serous retinopathy                | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Strabismus                        | 6                                                                       | 10         | 10          | 18         | 28                | 0                                                              | 0          |
|          | Subretinal fluid                  | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Sudden visual loss                | 1                                                                       | 2          | 0           | 1          | 3                 | 0                                                              | 0          |
|          | Swelling of eyelid                | 30                                                                      | 43         | 91          | 370        | 413               | 0                                                              | 0          |
|          | Swollen tear duct                 | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |

|                            |                                       | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------------------------|---------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|                            |                                       | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM                   | PT                                    | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|                            | Ulcerative keratitis                  | 1                                                                       | 7          | 0           | 0          | 7                 | 0                                                              | 0          |
|                            | Uveitis                               | 30                                                                      | 63         | 4           | 6          | 69                | 0                                                              | 0          |
|                            | Vision blurred                        | 388                                                                     | 592        | 608         | 1983       | 2575              | 0                                                              | 0          |
|                            | Visual acuity reduced                 | 22                                                                      | 25         | 19          | 31         | 56                | 0                                                              | 0          |
|                            | Visual acuity reduced transiently     | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|                            | Visual brightness                     | 0                                                                       | 0          | 0           | 6          | 6                 | 0                                                              | 0          |
|                            | Visual field defect                   | 36                                                                      | 62         | 27          | 61         | 123               | 0                                                              | 0          |
|                            | Visual impairment                     | 288                                                                     | 423        | 566         | 1280       | 1703              | 0                                                              | 0          |
|                            | Visual snow syndrome                  | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|                            | Vitreoretinal traction syndrome       | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                            | Vitreous adhesions                    | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|                            | Vitreous degeneration                 | 0                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                            | Vitreous detachment                   | 19                                                                      | 33         | 3           | 3          | 36                | 0                                                              | 0          |
|                            | Vitreous disorder                     | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|                            | Vitreous floaters                     | 23                                                                      | 39         | 33          | 135        | 174               | 0                                                              | 0          |
|                            | Vitreous haemorrhage                  | 9                                                                       | 12         | 0           | 0          | 12                | 0                                                              | 0          |
|                            | Vitreous opacities                    | 0                                                                       | 0          | 2           | 2          | 2                 | 0                                                              | 0          |
|                            | Vitritis                              | 0                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                            | Vogt-Koyanagi-Harada disease          | 5                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|                            | Xanthopsia                            | 2                                                                       | 2          | 3           | 4          | 6                 | 0                                                              | 0          |
| Gastrointestinal disorders | *** SOC TOTAL ***                     | 13509                                                                   | 19553      | 29247       | 89814      | 109367            | 2                                                              | 3          |
|                            | Abdominal adhesions                   | 0                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                            | Abdominal discomfort                  | 176                                                                     | 252        | 598         | 2379       | 2631              | 0                                                              | 0          |
|                            | Abdominal distension                  | 80                                                                      | 130        | 194         | 540        | 670               | 0                                                              | 0          |
|                            | Abdominal hernia                      | 3                                                                       | 4          | 0           | 2          | 6                 | 0                                                              | 0          |
|                            | Abdominal mass                        | 3                                                                       | 5          | 0           | 1          | 6                 | 0                                                              | 0          |
|                            | Abdominal migraine                    | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                            | Abdominal pain                        | 696                                                                     | 1012       | 1344        | 2900       | 3912              | 0                                                              | 0          |
|                            | Abdominal pain lower                  | 80                                                                      | 121        | 173         | 295        | 416               | 0                                                              | 0          |
|                            | Abdominal pain upper                  | 767                                                                     | 1012       | 910         | 2920       | 3932              | 0                                                              | 0          |
|                            | Abdominal rebound tenderness          | 1                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|                            | Abdominal rigidity                    | 4                                                                       | 6          | 6           | 22         | 28                | 0                                                              | 0          |
|                            | Abdominal symptom                     | 2                                                                       | 2          | 0           | 1          | 3                 | 0                                                              | 0          |
|                            | Abdominal tenderness                  | 6                                                                       | 13         | 9           | 30         | 43                | 0                                                              | 0          |
|                            | Abdominal wall haematoma              | 3                                                                       | 7          | 1           | 1          | 8                 | 0                                                              | 0          |
|                            | Abdominal wall haemorrhage            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                            | Abdominal wall mass                   | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                            | Abdominal wall oedema                 | 2                                                                       | 2          | 0           | 1          | 3                 | 0                                                              | 0          |
|                            | Abnormal faeces                       | 9                                                                       | 14         | 87          | 122        | 136               | 0                                                              | 0          |
|                            | Acetonaemic vomiting                  | 0                                                                       | 0          | 2           | 3          | 3                 | 0                                                              | 0          |
|                            | Achlorhydria                          | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|                            | Acquired oesophageal web              | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|                            | Acute abdomen                         | 3                                                                       | 7          | 0           | 0          | 7                 | 0                                                              | 0          |
|                            | Acute haemorrhagic ulcerative colitis | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                            | Aerophagia                            | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|                            | Anaesthesia oral                      | 3                                                                       | 5          | 8           | 16         | 21                | 0                                                              | 0          |
|                            | Anal blister                          | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|                            | Anal erythema                         | 1                                                                       | 1          | 1           | 2          | 3                 | 0                                                              | 0          |
|                            | Anal fistula                          | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |

|          |                                     | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|-------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                     | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                  | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Anal haemorrhage                    | 3                                                                       | 3          | 0           | 4          | 7                 | 0                                                              | 0          |
|          | Anal hypoaesthesia                  | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Anal incontinence                   | 20                                                                      | 43         | 24          | 62         | 105               | 0                                                              | 0          |
|          | Anal pruritus                       | 0                                                                       | 0          | 1           | 10         | 10                | 0                                                              | 0          |
|          | Anal sphincter atony                | 3                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Anal ulcer                          | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Angular cheilitis                   | 0                                                                       | 1          | 2           | 6          | 7                 | 0                                                              | 0          |
|          | Anorectal discomfort                | 2                                                                       | 3          | 3           | 9          | 12                | 0                                                              | 0          |
|          | Anorectal disorder                  | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Anorectal swelling                  | 0                                                                       | 1          | 1           | 2          | 3                 | 0                                                              | 0          |
|          | Aphthous ulcer                      | 12                                                                      | 17         | 58          | 149        | 166               | 0                                                              | 0          |
|          | Appendicolith                       | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Appendix disorder                   | 1                                                                       | 2          | 1           | 2          | 4                 | 0                                                              | 0          |
|          | Apyalism                            | 1                                                                       | 1          | 9           | 15         | 16                | 0                                                              | 0          |
|          | Ascites                             | 32                                                                      | 55         | 0           | 0          | 55                | 0                                                              | 0          |
|          | Atrophic glossitis                  | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Autoimmune pancreatitis             | 2                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Barrett's oesophagus                | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Bile acid malabsorption             | 0                                                                       | 0          | 1           | 3          | 3                 | 0                                                              | 0          |
|          | Biliary ascites                     | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Bowel movement irregularity         | 1                                                                       | 3          | 12          | 68         | 71                | 0                                                              | 0          |
|          | Breath odour                        | 4                                                                       | 6          | 11          | 17         | 23                | 0                                                              | 0          |
|          | Burning mouth syndrome              | 2                                                                       | 2          | 1           | 3          | 5                 | 0                                                              | 0          |
|          | Cardiospasm                         | 2                                                                       | 2          | 3           | 5          | 7                 | 0                                                              | 0          |
|          | Change of bowel habit               | 0                                                                       | 1          | 2           | 8          | 9                 | 0                                                              | 0          |
|          | Chapped lips                        | 1                                                                       | 1          | 14          | 65         | 66                | 0                                                              | 0          |
|          | Cheilitis                           | 4                                                                       | 8          | 15          | 84         | 92                | 0                                                              | 0          |
|          | Chronic gastritis                   | 0                                                                       | 2          | 0           | 1          | 3                 | 0                                                              | 0          |
|          | Coating in mouth                    | 1                                                                       | 1          | 1           | 9          | 10                | 0                                                              | 0          |
|          | Coeliac artery compression syndrome | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Coeliac artery stenosis             | 3                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Coeliac disease                     | 3                                                                       | 8          | 0           | 0          | 8                 | 0                                                              | 0          |
|          | Colitis                             | 42                                                                      | 72         | 12          | 42         | 114               | 0                                                              | 0          |
|          | Colitis ischaemic                   | 19                                                                      | 37         | 0           | 0          | 37                | 0                                                              | 0          |
|          | Colitis microscopic                 | 9                                                                       | 17         | 0           | 1          | 18                | 0                                                              | 0          |
|          | Colitis ulcerative                  | 55                                                                      | 94         | 5           | 9          | 103               | 0                                                              | 0          |
|          | Colonic fistula                     | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Constipation                        | 93                                                                      | 137        | 128         | 370        | 507               | 0                                                              | 0          |
|          | Crohn's disease                     | 26                                                                      | 52         | 5           | 10         | 62                | 0                                                              | 0          |
|          | Cyclic vomiting syndrome            | 1                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Defaecation disorder                | 1                                                                       | 1          | 2           | 8          | 9                 | 0                                                              | 0          |
|          | Defaecation urgency                 | 8                                                                       | 11         | 7           | 31         | 42                | 0                                                              | 0          |
|          | Dental caries                       | 3                                                                       | 4          | 3           | 8          | 12                | 0                                                              | 0          |
|          | Dental discomfort                   | 2                                                                       | 2          | 13          | 41         | 43                | 0                                                              | 0          |
|          | Dental paraesthesia                 | 4                                                                       | 4          | 7           | 11         | 15                | 0                                                              | 0          |
|          | Dental pulp disorder                | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Diaphragmatic hernia                | 2                                                                       | 2          | 0           | 1          | 3                 | 0                                                              | 0          |
|          | Diarrhoea                           | 1549                                                                    | 2099       | 3441        | 10673      | 12772             | 0                                                              | 0          |
|          | Diarrhoea haemorrhagic              | 19                                                                      | 80         | 5           | 9          | 89                | 0                                                              | 0          |

|          |                                             | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|---------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                             | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                          | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Diarrhoea neonatal                          | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Discoloured vomit                           | 5                                                                       | 7          | 1           | 9          | 16                | 0                                                              | 0          |
|          | Distal intestinal obstruction syndrome      | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Diverticular perforation                    | 5                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Diverticulum                                | 6                                                                       | 12         | 3           | 7          | 19                | 0                                                              | 0          |
|          | Diverticulum intestinal                     | 6                                                                       | 13         | 1           | 3          | 16                | 0                                                              | 0          |
|          | Diverticulum intestinal haemorrhagic        | 0                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Dry mouth                                   | 86                                                                      | 121        | 184         | 839        | 960               | 0                                                              | 0          |
|          | Duodenal ulcer                              | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Duodenal ulcer haemorrhage                  | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Duodenitis                                  | 4                                                                       | 8          | 0           | 0          | 8                 | 0                                                              | 0          |
|          | Duodenogastric reflux                       | 2                                                                       | 2          | 1           | 5          | 7                 | 0                                                              | 0          |
|          | Dysbiosis                                   | 2                                                                       | 2          | 0           | 1          | 3                 | 0                                                              | 0          |
|          | Dyschezia                                   | 3                                                                       | 3          | 5           | 13         | 16                | 0                                                              | 0          |
|          | Dyspepsia                                   | 150                                                                     | 189        | 239         | 613        | 802               | 0                                                              | 0          |
|          | Dysphagia                                   | 178                                                                     | 368        | 226         | 1317       | 1685              | 0                                                              | 0          |
|          | Enamel anomaly                              | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Enlarged uvula                              | 1                                                                       | 5          | 8           | 44         | 49                | 0                                                              | 0          |
|          | Enteric neuropathy                          | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Enteritis                                   | 10                                                                      | 17         | 4           | 11         | 28                | 0                                                              | 0          |
|          | Enterocolitis                               | 6                                                                       | 10         | 1           | 1          | 11                | 0                                                              | 0          |
|          | Enterocolitis haemorrhagic                  | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Enterocutaneous fistula                     | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Enterovesical fistula                       | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Eosinophilic colitis                        | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Eosinophilic oesophagitis                   | 1                                                                       | 1          | 1           | 3          | 4                 | 0                                                              | 0          |
|          | Epigastric discomfort                       | 6                                                                       | 12         | 9           | 19         | 31                | 0                                                              | 0          |
|          | Epiplonic appendagitis                      | 0                                                                       | 0          | 1           | 4          | 4                 | 0                                                              | 0          |
|          | Erosive oesophagitis                        | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Eructation                                  | 17                                                                      | 23         | 25          | 125        | 148               | 0                                                              | 0          |
|          | Faecal vomiting                             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Faecolith                                   | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Faecaloma                                   | 6                                                                       | 10         | 0           | 0          | 10                | 0                                                              | 0          |
|          | Faeces discoloured                          | 26                                                                      | 46         | 43          | 119        | 165               | 0                                                              | 0          |
|          | Faeces hard                                 | 2                                                                       | 2          | 2           | 7          | 9                 | 0                                                              | 0          |
|          | Faeces pale                                 | 0                                                                       | 1          | 3           | 13         | 14                | 0                                                              | 0          |
|          | Faeces soft                                 | 5                                                                       | 5          | 19          | 45         | 50                | 0                                                              | 0          |
|          | Flatulence                                  | 32                                                                      | 42         | 82          | 336        | 378               | 0                                                              | 0          |
|          | Food poisoning                              | 0                                                                       | 1          | 3           | 20         | 21                | 0                                                              | 0          |
|          | Food protein-induced enterocolitis syndrome | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Frequent bowel movements                    | 11                                                                      | 17         | 25          | 104        | 121               | 0                                                              | 0          |
|          | Functional gastrointestinal disorder        | 5                                                                       | 7          | 6           | 19         | 26                | 0                                                              | 0          |
|          | Gastric antral vascular ectasia             | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Gastric dilatation                          | 5                                                                       | 10         | 1           | 5          | 15                | 0                                                              | 0          |
|          | Gastric disorder                            | 5                                                                       | 8          | 10          | 33         | 41                | 0                                                              | 0          |
|          | Gastric haemorrhage                         | 5                                                                       | 9          | 0           | 0          | 9                 | 0                                                              | 0          |
|          | Gastric hypomotility                        | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Gastric mucosal lesion                      | 0                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Gastric perforation                         | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |

|          |                                    | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                    | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                 | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Gastric polyps                     | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Gastric ulcer                      | 7                                                                       | 16         | 0           | 2          | 18                | 0                                                              | 0          |
|          | Gastric ulcer haemorrhage          | 3                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Gastric ulcer perforation          | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Gastric varices                    | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Gastritis                          | 29                                                                      | 39         | 41          | 85         | 124               | 0                                                              | 0          |
|          | Gastritis erosive                  | 1                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Gastritis haemorrhagic             | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Gastrointestinal disorder          | 34                                                                      | 55         | 142         | 258        | 313               | 0                                                              | 0          |
|          | Gastrointestinal haemorrhage       | 45                                                                      | 115        | 1           | 2          | 117               | 0                                                              | 0          |
|          | Gastrointestinal hypermotility     | 1                                                                       | 1          | 1           | 4          | 5                 | 0                                                              | 0          |
|          | Gastrointestinal hypomotility      | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Gastrointestinal inflammation      | 15                                                                      | 21         | 9           | 15         | 36                | 0                                                              | 0          |
|          | Gastrointestinal motility disorder | 2                                                                       | 4          | 10          | 12         | 16                | 0                                                              | 0          |
|          | Gastrointestinal mucosal disorder  | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Gastrointestinal necrosis          | 3                                                                       | 6          | 0           | 0          | 6                 | 0                                                              | 0          |
|          | Gastrointestinal oedema            | 3                                                                       | 7          | 0           | 0          | 7                 | 0                                                              | 0          |
|          | Gastrointestinal pain              | 35                                                                      | 45         | 94          | 215        | 260               | 0                                                              | 0          |
|          | Gastrointestinal perforation       | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Gastrointestinal polyp             | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Gastrointestinal sounds abnormal   | 2                                                                       | 5          | 5           | 25         | 30                | 0                                                              | 0          |
|          | Gastrointestinal tract irritation  | 1                                                                       | 2          | 0           | 4          | 6                 | 0                                                              | 0          |
|          | Gastrointestinal ulcer             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Gastrointestinal wall thickening   | 5                                                                       | 12         | 1           | 2          | 14                | 0                                                              | 0          |
|          | Gastrooesophageal reflux disease   | 60                                                                      | 76         | 81          | 247        | 323               | 0                                                              | 0          |
|          | Gingival bleeding                  | 14                                                                      | 32         | 34          | 91         | 123               | 0                                                              | 0          |
|          | Gingival blister                   | 0                                                                       | 0          | 1           | 16         | 16                | 0                                                              | 0          |
|          | Gingival discolouration            | 1                                                                       | 2          | 4           | 10         | 12                | 0                                                              | 0          |
|          | Gingival discomfort                | 1                                                                       | 1          | 10          | 25         | 26                | 0                                                              | 0          |
|          | Gingival disorder                  | 3                                                                       | 3          | 5           | 6          | 9                 | 0                                                              | 0          |
|          | Gingival erythema                  | 0                                                                       | 2          | 2           | 12         | 14                | 0                                                              | 0          |
|          | Gingival oedema                    | 0                                                                       | 0          | 3           | 4          | 4                 | 0                                                              | 0          |
|          | Gingival pain                      | 20                                                                      | 21         | 41          | 128        | 149               | 0                                                              | 0          |
|          | Gingival pruritus                  | 0                                                                       | 0          | 1           | 9          | 9                 | 0                                                              | 0          |
|          | Gingival recession                 | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|          | Gingival swelling                  | 8                                                                       | 11         | 25          | 86         | 97                | 0                                                              | 0          |
|          | Gingival ulceration                | 0                                                                       | 0          | 1           | 4          | 4                 | 0                                                              | 0          |
|          | Glossitis                          | 8                                                                       | 10         | 8           | 42         | 52                | 0                                                              | 0          |
|          | Glossodynia                        | 14                                                                      | 20         | 42          | 220        | 240               | 0                                                              | 0          |
|          | Haematemesis                       | 41                                                                      | 94         | 1           | 6          | 100               | 0                                                              | 0          |
|          | Haematochezia                      | 97                                                                      | 217        | 18          | 26         | 243               | 0                                                              | 0          |
|          | Haemoperitoneum                    | 1                                                                       | 8          | 0           | 0          | 8                 | 0                                                              | 0          |
|          | Haemorrhagic ascites               | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Haemorrhoidal haemorrhage          | 0                                                                       | 0          | 6           | 13         | 13                | 0                                                              | 0          |
|          | Haemorrhoids                       | 10                                                                      | 13         | 31          | 64         | 77                | 0                                                              | 0          |
|          | Haemorrhoids thrombosed            | 3                                                                       | 4          | 17          | 22         | 26                | 0                                                              | 0          |
|          | Hiatus hernia                      | 18                                                                      | 35         | 4           | 12         | 47                | 0                                                              | 0          |
|          | Hyperaesthesia teeth               | 5                                                                       | 7          | 17          | 63         | 70                | 0                                                              | 0          |
|          | Hyperchlorhydria                   | 3                                                                       | 3          | 4           | 5          | 8                 | 0                                                              | 0          |

|          |                                    | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                    | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                 | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Hypertrophy of tongue papillae     | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|          | Hypoaesthesia oral                 | 95                                                                      | 178        | 256         | 1536       | 1714              | 0                                                              | 0          |
|          | Hypoaesthesia teeth                | 3                                                                       | 4          | 1           | 1          | 5                 | 0                                                              | 0          |
|          | Ileal perforation                  | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Ileus                              | 12                                                                      | 20         | 1           | 1          | 21                | 0                                                              | 0          |
|          | Ileus paralytic                    | 1                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Impaired gastric emptying          | 4                                                                       | 9          | 0           | 2          | 11                | 0                                                              | 0          |
|          | Incarcerated umbilical hernia      | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Infantile vomiting                 | 0                                                                       | 0          | 3           | 4          | 4                 | 0                                                              | 0          |
|          | Inflammatory bowel disease         | 10                                                                      | 15         | 1           | 2          | 17                | 0                                                              | 0          |
|          | Infrequent bowel movements         | 2                                                                       | 2          | 1           | 2          | 4                 | 0                                                              | 0          |
|          | Inguinal hernia                    | 4                                                                       | 7          | 0           | 2          | 9                 | 0                                                              | 0          |
|          | Internal hernia                    | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Intestinal angina                  | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Intestinal angioedema              | 0                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Intestinal atony                   | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Intestinal dilatation              | 2                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Intestinal haematoma               | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Intestinal haemorrhage             | 4                                                                       | 9          | 0           | 0          | 9                 | 0                                                              | 0          |
|          | Intestinal infarction              | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Intestinal ischaemia               | 7                                                                       | 21         | 0           | 0          | 21                | 0                                                              | 0          |
|          | Intestinal mass                    | 0                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Intestinal obstruction             | 20                                                                      | 38         | 2           | 4          | 42                | 0                                                              | 0          |
|          | Intestinal perforation             | 8                                                                       | 11         | 0           | 0          | 11                | 0                                                              | 0          |
|          | Intestinal pseudo-obstruction      | 2                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Intra-abdominal calcification      | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Intra-abdominal fluid collection   | 3                                                                       | 6          | 0           | 1          | 7                 | 0                                                              | 0          |
|          | Intra-abdominal haematoma          | 2                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Intra-abdominal haemorrhage        | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Intussusception                    | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Irritable bowel syndrome           | 10                                                                      | 14         | 19          | 59         | 73                | 0                                                              | 0          |
|          | Ischaemic enteritis                | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Large intestinal haemorrhage       | 2                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Large intestinal obstruction       | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Large intestinal stenosis          | 1                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Large intestinal ulcer             | 1                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Large intestinal ulcer haemorrhage | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Large intestine perforation        | 2                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 1          |
|          | Large intestine polyp              | 2                                                                       | 4          | 1           | 3          | 7                 | 0                                                              | 0          |
|          | Leukoplakia oral                   | 2                                                                       | 4          | 2           | 3          | 7                 | 0                                                              | 0          |
|          | Lip blister                        | 2                                                                       | 2          | 14          | 103        | 105               | 0                                                              | 0          |
|          | Lip discolouration                 | 4                                                                       | 4          | 13          | 31         | 35                | 0                                                              | 0          |
|          | Lip disorder                       | 3                                                                       | 5          | 6           | 41         | 46                | 0                                                              | 0          |
|          | Lip dry                            | 3                                                                       | 4          | 22          | 80         | 84                | 0                                                              | 0          |
|          | Lip erosion                        | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Lip erythema                       | 0                                                                       | 2          | 8           | 44         | 46                | 0                                                              | 0          |
|          | Lip exfoliation                    | 0                                                                       | 0          | 3           | 14         | 14                | 0                                                              | 0          |
|          | Lip haematoma                      | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Lip haemorrhage                    | 1                                                                       | 3          | 4           | 12         | 15                | 0                                                              | 0          |



|          |                                    | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                    | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                 | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Lip oedema                         | 19                                                                      | 35         | 48          | 77         | 112               | 0                                                              | 0          |
|          | Lip pain                           | 6                                                                       | 9          | 20          | 89         | 98                | 0                                                              | 0          |
|          | Lip pruritus                       | 5                                                                       | 12         | 13          | 108        | 120               | 0                                                              | 0          |
|          | Lip scab                           | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|          | Lip swelling                       | 145                                                                     | 255        | 358         | 1773       | 2028              | 0                                                              | 0          |
|          | Lip ulceration                     | 1                                                                       | 3          | 3           | 9          | 12                | 0                                                              | 0          |
|          | Loose tooth                        | 1                                                                       | 2          | 4           | 10         | 12                | 0                                                              | 0          |
|          | Lower gastrointestinal haemorrhage | 1                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Malabsorption                      | 0                                                                       | 0          | 1           | 5          | 5                 | 0                                                              | 0          |
|          | Mallory-Weiss syndrome             | 0                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Malocclusion                       | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Melaena                            | 34                                                                      | 50         | 0           | 0          | 50                | 0                                                              | 0          |
|          | Mesenteric arterial occlusion      | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Mesenteric artery thrombosis       | 3                                                                       | 7          | 0           | 0          | 7                 | 0                                                              | 0          |
|          | Mesenteric haemorrhage             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Mesenteric vein thrombosis         | 15                                                                      | 38         | 0           | 0          | 38                | 0                                                              | 0          |
|          | Mesenteric venous occlusion        | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Mesenteritis                       | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Mouth cyst                         | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Mouth haemorrhage                  | 17                                                                      | 35         | 22          | 42         | 77                | 0                                                              | 0          |
|          | Mouth swelling                     | 27                                                                      | 53         | 56          | 273        | 326               | 0                                                              | 0          |
|          | Mouth ulceration                   | 44                                                                      | 55         | 78          | 179        | 234               | 0                                                              | 0          |
|          | Mucous stools                      | 3                                                                       | 3          | 6           | 24         | 27                | 0                                                              | 0          |
|          | Nausea                             | 4861                                                                    | 6344       | 14299       | 39549      | 45893             | 1                                                              | 1          |
|          | Noninfective gingivitis            | 5                                                                       | 6          | 17          | 35         | 41                | 0                                                              | 0          |
|          | Noninfective sialoadenitis         | 1                                                                       | 1          | 0           | 4          | 5                 | 0                                                              | 0          |
|          | Obstruction gastric                | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Obstructive pancreatitis           | 4                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Odynophagia                        | 14                                                                      | 26         | 42          | 127        | 153               | 0                                                              | 0          |
|          | Oedema mouth                       | 2                                                                       | 2          | 2           | 8          | 10                | 0                                                              | 0          |
|          | Oedematous pancreatitis            | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Oesophageal achalasia              | 1                                                                       | 2          | 1           | 3          | 5                 | 0                                                              | 0          |
|          | Oesophageal compression            | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Oesophageal dilatation             | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Oesophageal discomfort             | 2                                                                       | 2          | 5           | 11         | 13                | 0                                                              | 0          |
|          | Oesophageal disorder               | 2                                                                       | 2          | 3           | 4          | 6                 | 0                                                              | 0          |
|          | Oesophageal food impaction         | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Oesophageal haemorrhage            | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Oesophageal irritation             | 0                                                                       | 0          | 5           | 5          | 5                 | 0                                                              | 0          |
|          | Oesophageal motility disorder      | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Oesophageal obstruction            | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Oesophageal oedema                 | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Oesophageal pain                   | 6                                                                       | 7          | 9           | 14         | 21                | 0                                                              | 0          |
|          | Oesophageal polyp                  | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Oesophageal rupture                | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Oesophageal spasm                  | 2                                                                       | 3          | 1           | 11         | 14                | 0                                                              | 0          |
|          | Oesophageal stenosis               | 2                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Oesophageal ulcer                  | 2                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Oesophageal varices haemorrhage    | 1                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |

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|----------|-------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                               | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                            | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Oesophagitis                  | 7                                                                       | 10         | 9           | 16         | 26                | 0                                                              | 0          |
|          | Omental haemorrhage           | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Omental infarction            | 1                                                                       | 1          | 0           | 2          | 3                 | 0                                                              | 0          |
|          | Omental necrosis              | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Oral blood blister            | 3                                                                       | 12         | 6           | 9          | 21                | 0                                                              | 0          |
|          | Oral discharge                | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|          | Oral discomfort               | 21                                                                      | 30         | 98          | 307        | 337               | 0                                                              | 0          |
|          | Oral disorder                 | 9                                                                       | 15         | 15          | 44         | 59                | 0                                                              | 0          |
|          | Oral dysaesthesia             | 1                                                                       | 1          | 7           | 12         | 13                | 0                                                              | 0          |
|          | Oral hyperaesthesia           | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Oral lichen planus            | 1                                                                       | 2          | 3           | 6          | 8                 | 0                                                              | 0          |
|          | Oral mucosa erosion           | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Oral mucosa haematoma         | 0                                                                       | 1          | 3           | 3          | 4                 | 0                                                              | 0          |
|          | Oral mucosal blistering       | 8                                                                       | 20         | 46          | 140        | 160               | 0                                                              | 0          |
|          | Oral mucosal discolouration   | 0                                                                       | 1          | 2           | 3          | 4                 | 0                                                              | 0          |
|          | Oral mucosal eruption         | 5                                                                       | 9          | 9           | 46         | 55                | 0                                                              | 0          |
|          | Oral mucosal erythema         | 3                                                                       | 4          | 10          | 33         | 37                | 0                                                              | 0          |
|          | Oral mucosal exfoliation      | 3                                                                       | 4          | 3           | 10         | 14                | 0                                                              | 0          |
|          | Oral mucosal roughening       | 0                                                                       | 1          | 0           | 4          | 5                 | 0                                                              | 0          |
|          | Oral pain                     | 17                                                                      | 28         | 86          | 300        | 328               | 0                                                              | 0          |
|          | Oral pigmentation             | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Oral pruritus                 | 4                                                                       | 9          | 15          | 126        | 135               | 0                                                              | 0          |
|          | Oral purpura                  | 0                                                                       | 3          | 0           | 1          | 4                 | 0                                                              | 0          |
|          | Palatal disorder              | 0                                                                       | 0          | 1           | 5          | 5                 | 0                                                              | 0          |
|          | Palatal oedema                | 4                                                                       | 7          | 5           | 9          | 16                | 0                                                              | 0          |
|          | Palatal swelling              | 2                                                                       | 5          | 8           | 25         | 30                | 0                                                              | 0          |
|          | Pancreatic atrophy            | 5                                                                       | 6          | 0           | 0          | 6                 | 0                                                              | 0          |
|          | Pancreatic cyst               | 2                                                                       | 3          | 2           | 2          | 5                 | 0                                                              | 0          |
|          | Pancreatic disorder           | 0                                                                       | 2          | 1           | 3          | 5                 | 0                                                              | 0          |
|          | Pancreatic duct dilatation    | 3                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Pancreatic duct stenosis      | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Pancreatic enlargement        | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Pancreatic enzyme abnormality | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Pancreatic failure            | 3                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Pancreatic mass               | 1                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Pancreatic pseudocyst         | 0                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Pancreatitis                  | 66                                                                      | 112        | 5           | 6          | 118               | 0                                                              | 0          |
|          | Pancreatitis acute            | 34                                                                      | 85         | 1           | 1          | 86                | 0                                                              | 0          |
|          | Pancreatitis chronic          | 2                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Pancreatitis necrotising      | 2                                                                       | 6          | 0           | 0          | 6                 | 0                                                              | 0          |
|          | Paraesthesia oral             | 111                                                                     | 201        | 310         | 2288       | 2489              | 0                                                              | 0          |
|          | Parotid duct obstruction      | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Parotid gland enlargement     | 1                                                                       | 3          | 6           | 14         | 17                | 0                                                              | 0          |
|          | Pelvic floor dysfunction      | 2                                                                       | 2          | 1           | 1          | 3                 | 0                                                              | 0          |
|          | Peptic ulcer                  | 2                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Peptic ulcer haemorrhage      | 1                                                                       | 3          | 1           | 2          | 5                 | 0                                                              | 0          |
|          | Periodontal disease           | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Peritoneal disorder           | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Peritoneal fibrosis           | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |

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|----------|-------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                     | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                  | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Pigmentation lip                    | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Plicated tongue                     | 0                                                                       | 0          | 1           | 4          | 4                 | 0                                                              | 0          |
|          | Pneumatosis intestinalis            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Pneumoperitoneum                    | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Portal hypertensive colopathy       | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Post-tussive vomiting               | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Pouchitis                           | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Proctalgia                          | 9                                                                       | 9          | 8           | 20         | 29                | 0                                                              | 0          |
|          | Proctitis                           | 2                                                                       | 2          | 2           | 3          | 5                 | 0                                                              | 0          |
|          | Proctitis ulcerative                | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Protrusion tongue                   | 2                                                                       | 2          | 0           | 1          | 3                 | 0                                                              | 0          |
|          | Pseudodiverticular disease          | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Rectal discharge                    | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|          | Rectal fissure                      | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Rectal haemorrhage                  | 50                                                                      | 117        | 10          | 11         | 128               | 0                                                              | 0          |
|          | Rectal lesion                       | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Rectal tenesmus                     | 1                                                                       | 1          | 0           | 5          | 6                 | 0                                                              | 0          |
|          | Reflux gastritis                    | 0                                                                       | 0          | 2           | 12         | 12                | 0                                                              | 0          |
|          | Regurgitation                       | 4                                                                       | 6          | 5           | 14         | 20                | 0                                                              | 0          |
|          | Retching                            | 66                                                                      | 97         | 111         | 591        | 688               | 0                                                              | 0          |
|          | Retroperitoneal effusion            | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Retroperitoneal haematoma           | 2                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Retroperitoneal haemorrhage         | 2                                                                       | 8          | 0           | 0          | 8                 | 0                                                              | 0          |
|          | Retroperitoneal mass                | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Retroperitoneal oedema              | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Saliva altered                      | 2                                                                       | 2          | 3           | 10         | 12                | 0                                                              | 0          |
|          | Saliva discolouration               | 1                                                                       | 1          | 2           | 2          | 3                 | 0                                                              | 0          |
|          | Salivary gland disorder             | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|          | Salivary gland enlargement          | 0                                                                       | 0          | 5           | 15         | 15                | 0                                                              | 0          |
|          | Salivary gland mass                 | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Salivary gland mucocoele            | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|          | Salivary gland pain                 | 3                                                                       | 3          | 2           | 3          | 6                 | 0                                                              | 0          |
|          | Salivary hypersecretion             | 13                                                                      | 18         | 15          | 98         | 116               | 0                                                              | 0          |
|          | Scalloped tongue                    | 0                                                                       | 0          | 1           | 5          | 5                 | 0                                                              | 0          |
|          | Short-bowel syndrome                | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Small intestinal haemorrhage        | 2                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Small intestinal obstruction        | 9                                                                       | 34         | 0           | 0          | 34                | 0                                                              | 0          |
|          | Small intestinal perforation        | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Small intestinal ulcer haemorrhage  | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Splenic artery aneurysm             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Stasis syndrome                     | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Stiff tongue                        | 0                                                                       | 0          | 2           | 6          | 6                 | 0                                                              | 0          |
|          | Stomach mass                        | 1                                                                       | 1          | 0           | 2          | 3                 | 0                                                              | 0          |
|          | Stomatitis                          | 26                                                                      | 35         | 74          | 275        | 310               | 0                                                              | 0          |
|          | Strawberry tongue                   | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Subileus                            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Submaxillary gland enlargement      | 2                                                                       | 2          | 4           | 7          | 9                 | 0                                                              | 0          |
|          | Superior mesenteric artery syndrome | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Swollen tongue                      | 118                                                                     | 284        | 171         | 1322       | 1606              | 0                                                              | 0          |

|                                                     |                                         | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|-----------------------------------------------------|-----------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|                                                     |                                         | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM                                            | PT                                      | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|                                                     | Teeth brittle                           | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|                                                     | Teething                                | 0                                                                       | 0          | 5           | 9          | 9                 | 0                                                              | 0          |
|                                                     | Terminal ileitis                        | 2                                                                       | 6          | 0           | 0          | 6                 | 0                                                              | 0          |
|                                                     | Tongue atrophy                          | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                                                     | Tongue blistering                       | 2                                                                       | 5          | 14          | 62         | 67                | 0                                                              | 0          |
|                                                     | Tongue coated                           | 3                                                                       | 3          | 5           | 20         | 23                | 0                                                              | 0          |
|                                                     | Tongue discolouration                   | 2                                                                       | 7          | 17          | 72         | 79                | 0                                                              | 0          |
|                                                     | Tongue discomfort                       | 8                                                                       | 16         | 57          | 221        | 237               | 0                                                              | 0          |
|                                                     | Tongue disorder                         | 8                                                                       | 15         | 11          | 184        | 199               | 0                                                              | 0          |
|                                                     | Tongue dry                              | 3                                                                       | 5          | 9           | 33         | 38                | 0                                                              | 0          |
|                                                     | Tongue eruption                         | 0                                                                       | 0          | 6           | 24         | 24                | 0                                                              | 0          |
|                                                     | Tongue erythema                         | 3                                                                       | 8          | 6           | 45         | 53                | 0                                                              | 0          |
|                                                     | Tongue exfoliation                      | 1                                                                       | 1          | 1           | 7          | 8                 | 0                                                              | 0          |
|                                                     | Tongue geographic                       | 1                                                                       | 1          | 5           | 6          | 7                 | 0                                                              | 0          |
|                                                     | Tongue haematoma                        | 0                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|                                                     | Tongue haemorrhage                      | 1                                                                       | 3          | 2           | 7          | 10                | 0                                                              | 0          |
|                                                     | Tongue induration                       | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|                                                     | Tongue movement disturbance             | 5                                                                       | 11         | 3           | 9          | 20                | 0                                                              | 0          |
|                                                     | Tongue oedema                           | 17                                                                      | 24         | 24          | 50         | 74                | 0                                                              | 0          |
|                                                     | Tongue pigmentation                     | 0                                                                       | 0          | 0           | 3          | 3                 | 0                                                              | 0          |
|                                                     | Tongue pruritus                         | 5                                                                       | 16         | 9           | 128        | 144               | 0                                                              | 0          |
|                                                     | Tongue rough                            | 0                                                                       | 0          | 2           | 8          | 8                 | 0                                                              | 0          |
|                                                     | Tongue spasm                            | 2                                                                       | 2          | 2           | 8          | 10                | 0                                                              | 0          |
|                                                     | Tongue thrust                           | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|                                                     | Tongue ulceration                       | 2                                                                       | 7          | 8           | 35         | 42                | 0                                                              | 0          |
|                                                     | Tooth discolouration                    | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|                                                     | Tooth disorder                          | 2                                                                       | 3          | 7           | 23         | 26                | 0                                                              | 0          |
|                                                     | Tooth loss                              | 1                                                                       | 1          | 3           | 12         | 13                | 0                                                              | 0          |
|                                                     | Tooth resorption                        | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|                                                     | Toothache                               | 29                                                                      | 44         | 160         | 394        | 438               | 0                                                              | 0          |
|                                                     | Trichoglossia                           | 0                                                                       | 0          | 3           | 6          | 6                 | 0                                                              | 0          |
|                                                     | Truncus coeliacus thrombosis            | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                                                     | Ulcerative gastritis                    | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|                                                     | Umbilical hernia                        | 4                                                                       | 6          | 1           | 2          | 8                 | 0                                                              | 0          |
|                                                     | Upper gastrointestinal haemorrhage      | 16                                                                      | 22         | 0           | 0          | 22                | 0                                                              | 0          |
|                                                     | Uvulitis                                | 0                                                                       | 0          | 0           | 3          | 3                 | 0                                                              | 0          |
|                                                     | Varices oesophageal                     | 3                                                                       | 3          | 0           | 1          | 4                 | 0                                                              | 0          |
|                                                     | Vasculitis gastrointestinal             | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                                     | Visceral venous thrombosis              | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                                     | Volvulus                                | 6                                                                       | 10         | 0           | 0          | 10                | 0                                                              | 0          |
|                                                     | Vomiting                                | 2365                                                                    | 3359       | 3756        | 11795      | 15154             | 1                                                              | 1          |
|                                                     | Vomiting projectile                     | 17                                                                      | 22         | 6           | 40         | 62                | 0                                                              | 0          |
| General disorders and administration site condition | *** SOC TOTAL ***                       | 47831                                                                   | 65651      | 240541      | 618058     | 683709            | 6                                                              | 7          |
|                                                     | Abscess sterile                         | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|                                                     | Absence of immediate treatment response | 0                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|                                                     | Acute phase reaction                    | 0                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                                                     | Adhesion                                | 1                                                                       | 2          | 4           | 4          | 6                 | 0                                                              | 0          |
|                                                     | Administration site bruise              | 1                                                                       | 1          | 5           | 16         | 17                | 0                                                              | 0          |
|                                                     | Administration site coldness            | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |

|          |                                               | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|-----------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                               | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                            | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Administration site discolouration            | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|          | Administration site discomfort                | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|          | Administration site dysaesthesia              | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Administration site erythema                  | 3                                                                       | 3          | 33          | 55         | 58                | 0                                                              | 0          |
|          | Administration site extravasation             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Administration site haematoma                 | 1                                                                       | 1          | 3           | 3          | 4                 | 0                                                              | 0          |
|          | Administration site hyperaesthesia            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Administration site hypersensitivity          | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Administration site hypoaesthesia             | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Administration site indentation               | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Administration site induration                | 0                                                                       | 1          | 3           | 5          | 6                 | 0                                                              | 0          |
|          | Administration site inflammation              | 0                                                                       | 1          | 6           | 9          | 10                | 0                                                              | 0          |
|          | Administration site irritation                | 0                                                                       | 0          | 2           | 3          | 3                 | 0                                                              | 0          |
|          | Administration site joint movement impairment | 0                                                                       | 0          | 2           | 3          | 3                 | 0                                                              | 0          |
|          | Administration site joint pain                | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Administration site lymphadenopathy           | 1                                                                       | 1          | 7           | 10         | 11                | 0                                                              | 0          |
|          | Administration site macule                    | 0                                                                       | 0          | 2           | 3          | 3                 | 0                                                              | 0          |
|          | Administration site movement impairment       | 1                                                                       | 1          | 6           | 10         | 11                | 0                                                              | 0          |
|          | Administration site nodule                    | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Administration site oedema                    | 3                                                                       | 4          | 13          | 18         | 22                | 0                                                              | 0          |
|          | Administration site pain                      | 10                                                                      | 20         | 122         | 160        | 180               | 0                                                              | 0          |
|          | Administration site papule                    | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|          | Administration site paraesthesia              | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Administration site plaque                    | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Administration site pruritus                  | 1                                                                       | 1          | 8           | 15         | 16                | 0                                                              | 0          |
|          | Administration site rash                      | 1                                                                       | 1          | 11          | 17         | 18                | 0                                                              | 0          |
|          | Administration site reaction                  | 2                                                                       | 2          | 27          | 41         | 43                | 0                                                              | 0          |
|          | Administration site swelling                  | 2                                                                       | 3          | 15          | 22         | 25                | 0                                                              | 0          |
|          | Administration site urticaria                 | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Administration site warmth                    | 0                                                                       | 0          | 14          | 27         | 27                | 0                                                              | 0          |
|          | Adverse drug reaction                         | 87                                                                      | 99         | 70          | 192        | 291               | 0                                                              | 0          |
|          | Adverse event                                 | 24                                                                      | 29         | 86          | 371        | 400               | 0                                                              | 0          |
|          | Adverse food reaction                         | 0                                                                       | 0          | 0           | 3          | 3                 | 0                                                              | 0          |
|          | Adverse reaction                              | 18                                                                      | 30         | 82          | 417        | 447               | 0                                                              | 0          |
|          | Agonal death struggle                         | 0                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Alcohol interaction                           | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Application site acne                         | 0                                                                       | 0          | 2           | 2          | 2                 | 0                                                              | 0          |
|          | Application site bruise                       | 1                                                                       | 1          | 5           | 5          | 6                 | 0                                                              | 0          |
|          | Application site burn                         | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Application site coldness                     | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Application site discolouration               | 0                                                                       | 0          | 4           | 4          | 4                 | 0                                                              | 0          |
|          | Application site eczema                       | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|          | Application site erythema                     | 8                                                                       | 10         | 391         | 472        | 482               | 0                                                              | 0          |
|          | Application site fibrosis                     | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Application site haematoma                    | 1                                                                       | 2          | 2           | 3          | 5                 | 0                                                              | 0          |
|          | Application site hypersensitivity             | 1                                                                       | 1          | 6           | 8          | 9                 | 0                                                              | 0          |
|          | Application site hypoaesthesia                | 1                                                                       | 1          | 7           | 7          | 8                 | 0                                                              | 0          |
|          | Application site induration                   | 0                                                                       | 0          | 11          | 13         | 13                | 0                                                              | 0          |
|          | Application site inflammation                 | 1                                                                       | 1          | 7           | 7          | 8                 | 0                                                              | 0          |

|          |                                             | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|---------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                             | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                          | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Application site joint erythema             | 0                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Application site joint pain                 | 0                                                                       | 0          | 3           | 4          | 4                 | 0                                                              | 0          |
|          | Application site joint swelling             | 1                                                                       | 1          | 2           | 3          | 4                 | 0                                                              | 0          |
|          | Application site lymphadenopathy            | 0                                                                       | 0          | 4           | 7          | 7                 | 0                                                              | 0          |
|          | Application site movement impairment        | 0                                                                       | 0          | 9           | 11         | 11                | 0                                                              | 0          |
|          | Application site necrosis                   | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Application site nerve damage               | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Application site oedema                     | 0                                                                       | 0          | 2           | 3          | 3                 | 0                                                              | 0          |
|          | Application site pain                       | 6                                                                       | 7          | 865         | 1047       | 1054              | 0                                                              | 0          |
|          | Application site papules                    | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Application site paraesthesia               | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Application site plaque                     | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|          | Application site pruritus                   | 2                                                                       | 3          | 93          | 111        | 114               | 0                                                              | 0          |
|          | Application site rash                       | 0                                                                       | 0          | 14          | 17         | 17                | 0                                                              | 0          |
|          | Application site reaction                   | 1                                                                       | 1          | 193         | 226        | 227               | 0                                                              | 0          |
|          | Application site scar                       | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Application site swelling                   | 3                                                                       | 4          | 331         | 385        | 389               | 0                                                              | 0          |
|          | Application site urticaria                  | 0                                                                       | 0          | 2           | 2          | 2                 | 0                                                              | 0          |
|          | Application site vasculitis                 | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Application site vesicles                   | 0                                                                       | 0          | 4           | 7          | 7                 | 0                                                              | 0          |
|          | Application site warmth                     | 0                                                                       | 0          | 33          | 40         | 40                | 0                                                              | 0          |
|          | Asthenia                                    | 2082                                                                    | 3179       | 4137        | 12517      | 15696             | 0                                                              | 0          |
|          | Atrophy                                     | 8                                                                       | 10         | 3           | 5          | 15                | 0                                                              | 0          |
|          | Axillary pain                               | 480                                                                     | 577        | 990         | 2859       | 3436              | 0                                                              | 0          |
|          | Brain death                                 | 8                                                                       | 15         | 0           | 0          | 15                | 0                                                              | 0          |
|          | Breakthrough pain                           | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Calcinosis                                  | 1                                                                       | 1          | 1           | 3          | 4                 | 0                                                              | 0          |
|          | Capsular contracture associated with breast | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Cardiac complication associated with device | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Cardiac death                               | 3                                                                       | 9          | 0           | 0          | 9                 | 0                                                              | 0          |
|          | Catheter site haemorrhage                   | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Challenge site reaction                     | 0                                                                       | 0          | 3           | 3          | 3                 | 0                                                              | 0          |
|          | Chest discomfort                            | 978                                                                     | 1386       | 1490        | 4334       | 5720              | 0                                                              | 0          |
|          | Chest pain                                  | 2883                                                                    | 3961       | 2613        | 5279       | 9240              | 0                                                              | 0          |
|          | Chills                                      | 4696                                                                    | 5952       | 19486       | 56441      | 62393             | 1                                                              | 1          |
|          | Chronic disease                             | 3                                                                       | 4          | 0           | 1          | 5                 | 0                                                              | 0          |
|          | Chronic fatigue syndrome                    | 13                                                                      | 13         | 11          | 20         | 33                | 0                                                              | 0          |
|          | Clinical death                              | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Complication associated with device         | 4                                                                       | 10         | 0           | 6          | 16                | 0                                                              | 0          |
|          | Complication of device insertion            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Complication of device removal              | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Concomitant disease aggravated              | 8                                                                       | 9          | 12          | 16         | 25                | 0                                                              | 0          |
|          | Condition aggravated                        | 978                                                                     | 1517       | 722         | 2348       | 3865              | 0                                                              | 0          |
|          | Contrast media deposition                   | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Crepitations                                | 7                                                                       | 12         | 3           | 13         | 25                | 0                                                              | 0          |
|          | Critical illness                            | 3                                                                       | 9          | 0           | 0          | 9                 | 0                                                              | 0          |
|          | Crying                                      | 30                                                                      | 45         | 67          | 234        | 279               | 0                                                              | 0          |
|          | Cyst                                        | 10                                                                      | 15         | 26          | 64         | 79                | 0                                                              | 0          |
|          | Cyst rupture                                | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |

|          |                                       | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|---------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                       | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                    | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Death                                 | 1078                                                                    | 2721       | 0           | 0          | 2721              | 0                                                              | 0          |
|          | Death neonatal                        | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Decreased activity                    | 10                                                                      | 15         | 20          | 52         | 67                | 0                                                              | 0          |
|          | Decreased gait velocity               | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Deformity                             | 2                                                                       | 2          | 2           | 6          | 8                 | 0                                                              | 0          |
|          | Dehiscence                            | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Developmental delay                   | 0                                                                       | 1          | 0           | 2          | 3                 | 0                                                              | 0          |
|          | Device embolisation                   | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Device intolerance                    | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Diet failure                          | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Discharge                             | 4                                                                       | 6          | 13          | 35         | 41                | 0                                                              | 0          |
|          | Discomfort                            | 176                                                                     | 249        | 501         | 1621       | 1870              | 0                                                              | 0          |
|          | Disease prodromal stage               | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|          | Disease progression                   | 6                                                                       | 12         | 0           | 0          | 12                | 0                                                              | 0          |
|          | Disease recurrence                    | 31                                                                      | 33         | 23          | 34         | 67                | 0                                                              | 0          |
|          | Disease susceptibility                | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Drowning                              | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Drug ineffective                      | 93                                                                      | 104        | 975         | 1296       | 1400              | 0                                                              | 0          |
|          | Drug interaction                      | 10                                                                      | 15         | 21          | 55         | 70                | 0                                                              | 0          |
|          | Drug intolerance                      | 3                                                                       | 4          | 0           | 2          | 6                 | 0                                                              | 0          |
|          | Drug tolerance                        | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Drug tolerance decreased              | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Drug withdrawal syndrome              | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Dysplasia                             | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Early satiety                         | 1                                                                       | 1          | 0           | 2          | 3                 | 0                                                              | 0          |
|          | Effusion                              | 10                                                                      | 13         | 2           | 6          | 19                | 0                                                              | 0          |
|          | Embolia cutis medicamentosa           | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Enanthema                             | 1                                                                       | 1          | 1           | 2          | 3                 | 0                                                              | 0          |
|          | Encapsulation reaction                | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Energy increased                      | 3                                                                       | 3          | 16          | 65         | 68                | 0                                                              | 0          |
|          | Exercise tolerance decreased          | 62                                                                      | 66         | 83          | 124        | 190               | 0                                                              | 0          |
|          | Extensive swelling of vaccinated limb | 155                                                                     | 206        | 884         | 1659       | 1865              | 0                                                              | 0          |
|          | Extravasation                         | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Face oedema                           | 40                                                                      | 63         | 97          | 185        | 248               | 0                                                              | 0          |
|          | Facial discomfort                     | 4                                                                       | 7          | 34          | 121        | 128               | 0                                                              | 0          |
|          | Facial pain                           | 60                                                                      | 82         | 117         | 461        | 543               | 0                                                              | 0          |
|          | Fat necrosis                          | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Fat tissue decreased                  | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Fatigue                               | 6896                                                                    | 8746       | 28225       | 68089      | 76835             | 3                                                              | 3          |
|          | Feeling abnormal                      | 730                                                                     | 1049       | 5421        | 11470      | 12519             | 0                                                              | 0          |
|          | Feeling cold                          | 348                                                                     | 413        | 1750        | 3798       | 4211              | 0                                                              | 0          |
|          | Feeling drunk                         | 14                                                                      | 24         | 29          | 106        | 130               | 0                                                              | 0          |
|          | Feeling hot                           | 360                                                                     | 487        | 2288        | 6063       | 6550              | 0                                                              | 0          |
|          | Feeling jittery                       | 16                                                                      | 24         | 29          | 191        | 215               | 0                                                              | 0          |
|          | Feeling of body temperature change    | 115                                                                     | 148        | 187         | 560        | 708               | 0                                                              | 0          |
|          | Feeling of relaxation                 | 0                                                                       | 0          | 1           | 31         | 31                | 0                                                              | 0          |
|          | Fever neonatal                        | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Fibrosis                              | 4                                                                       | 7          | 3           | 4          | 11                | 0                                                              | 0          |
|          | Foaming at mouth                      | 9                                                                       | 25         | 6           | 20         | 45                | 0                                                              | 0          |

|          |                                         | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|-----------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                         | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                      | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Food interaction                        | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Foreign body reaction                   | 0                                                                       | 0          | 2           | 2          | 2                 | 0                                                              | 0          |
|          | Gait deviation                          | 2                                                                       | 2          | 0           | 1          | 3                 | 0                                                              | 0          |
|          | Gait disturbance                        | 412                                                                     | 735        | 624         | 2235       | 2970              | 0                                                              | 0          |
|          | Gait inability                          | 192                                                                     | 373        | 150         | 523        | 896               | 0                                                              | 0          |
|          | General physical health deterioration   | 172                                                                     | 274        | 140         | 201        | 475               | 0                                                              | 0          |
|          | General symptom                         | 6                                                                       | 8          | 4           | 22         | 30                | 0                                                              | 0          |
|          | Generalised oedema                      | 15                                                                      | 21         | 15          | 26         | 47                | 0                                                              | 0          |
|          | Glassy eyes                             | 3                                                                       | 3          | 6           | 38         | 41                | 0                                                              | 0          |
|          | Granuloma                               | 7                                                                       | 9          | 3           | 6          | 15                | 0                                                              | 0          |
|          | Gravitational oedema                    | 1                                                                       | 2          | 1           | 1          | 3                 | 0                                                              | 0          |
|          | Hangover                                | 17                                                                      | 21         | 10          | 34         | 55                | 0                                                              | 0          |
|          | Hernia                                  | 5                                                                       | 6          | 2           | 8          | 14                | 0                                                              | 0          |
|          | Hernia pain                             | 4                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | High-pitched crying                     | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Hunger                                  | 12                                                                      | 15         | 38          | 97         | 112               | 0                                                              | 0          |
|          | Hyperplasia                             | 0                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Hyperpyrexia                            | 281                                                                     | 470        | 66          | 85         | 555               | 0                                                              | 0          |
|          | Hyperthermia                            | 21                                                                      | 27         | 36          | 55         | 82                | 0                                                              | 0          |
|          | Hyperthermia malignant                  | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Hypertrophy                             | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Hypothermia                             | 42                                                                      | 75         | 11          | 18         | 93                | 0                                                              | 0          |
|          | Idiosyncratic drug reaction             | 1                                                                       | 2          | 1           | 2          | 4                 | 0                                                              | 0          |
|          | Ill-defined disorder                    | 5                                                                       | 9          | 9           | 25         | 34                | 0                                                              | 0          |
|          | Illness                                 | 513                                                                     | 633        | 1225        | 2675       | 3308              | 0                                                              | 0          |
|          | Immediate post-injection reaction       | 74                                                                      | 144        | 65          | 1113       | 1257              | 0                                                              | 0          |
|          | Impaired healing                        | 7                                                                       | 9          | 16          | 27         | 36                | 0                                                              | 0          |
|          | Impaired self-care                      | 15                                                                      | 18         | 1           | 5          | 23                | 0                                                              | 0          |
|          | Implant site hyperaesthesia             | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Implant site hypersensitivity           | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Implant site induration                 | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Implant site inflammation               | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Implant site pain                       | 0                                                                       | 0          | 0           | 3          | 3                 | 0                                                              | 0          |
|          | Implant site paraesthesia               | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|          | Implant site swelling                   | 0                                                                       | 0          | 5           | 6          | 6                 | 0                                                              | 0          |
|          | Implant site warmth                     | 1                                                                       | 2          | 0           | 1          | 3                 | 0                                                              | 0          |
|          | Inadequate analgesia                    | 2                                                                       | 2          | 1           | 1          | 3                 | 0                                                              | 0          |
|          | Induration                              | 18                                                                      | 23         | 147         | 1275       | 1298              | 0                                                              | 0          |
|          | Inflammation                            | 226                                                                     | 325        | 412         | 1095       | 1420              | 0                                                              | 0          |
|          | Inflammatory pain                       | 5                                                                       | 6          | 9           | 9          | 15                | 0                                                              | 0          |
|          | Influenza like illness                  | 935                                                                     | 1190       | 4129        | 8579       | 9769              | 0                                                              | 0          |
|          | Infusion site bruising                  | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Infusion site erythema                  | 0                                                                       | 0          | 6           | 7          | 7                 | 0                                                              | 0          |
|          | Infusion site joint erythema            | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Infusion site joint inflammation        | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Infusion site joint movement impairment | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Infusion site joint pain                | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Infusion site joint swelling            | 0                                                                       | 0          | 1           | 4          | 4                 | 0                                                              | 0          |
|          | Infusion site mobility decreased        | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |



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|          |                                          | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                       | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Infusion site oedema                     | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Infusion site pain                       | 2                                                                       | 3          | 1           | 5          | 8                 | 0                                                              | 0          |
|          | Infusion site pruritus                   | 2                                                                       | 2          | 3           | 6          | 8                 | 0                                                              | 0          |
|          | Infusion site rash                       | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Infusion site reaction                   | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|          | Infusion site urticaria                  | 1                                                                       | 1          | 2           | 3          | 4                 | 0                                                              | 0          |
|          | Infusion site warmth                     | 0                                                                       | 0          | 1           | 5          | 5                 | 0                                                              | 0          |
|          | Inhibitory drug interaction              | 0                                                                       | 0          | 3           | 6          | 6                 | 0                                                              | 0          |
|          | Injected limb mobility decreased         | 85                                                                      | 136        | 195         | 770        | 906               | 0                                                              | 0          |
|          | Injection site atrophy                   | 0                                                                       | 0          | 3           | 3          | 3                 | 0                                                              | 0          |
|          | Injection site bruising                  | 18                                                                      | 23         | 45          | 682        | 705               | 0                                                              | 0          |
|          | Injection site coldness                  | 0                                                                       | 0          | 0           | 6          | 6                 | 0                                                              | 0          |
|          | Injection site cyst                      | 1                                                                       | 1          | 2           | 9          | 10                | 0                                                              | 0          |
|          | Injection site dermatitis                | 1                                                                       | 1          | 1           | 3          | 4                 | 0                                                              | 0          |
|          | Injection site discharge                 | 0                                                                       | 0          | 1           | 8          | 8                 | 0                                                              | 0          |
|          | Injection site discolouration            | 0                                                                       | 1          | 16          | 277        | 278               | 0                                                              | 0          |
|          | Injection site discomfort                | 3                                                                       | 5          | 154         | 550        | 555               | 0                                                              | 0          |
|          | Injection site dryness                   | 0                                                                       | 0          | 0           | 9          | 9                 | 0                                                              | 0          |
|          | Injection site dysaesthesia              | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Injection site eczema                    | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Injection site erosion                   | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|          | Injection site erythema                  | 230                                                                     | 318        | 7079        | 25520      | 25838             | 0                                                              | 0          |
|          | Injection site exfoliation               | 0                                                                       | 0          | 3           | 9          | 9                 | 0                                                              | 0          |
|          | Injection site extravasation             | 1                                                                       | 1          | 10          | 50         | 51                | 0                                                              | 0          |
|          | Injection site fibrosis                  | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Injection site granuloma                 | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Injection site haematoma                 | 5                                                                       | 7          | 684         | 1238       | 1245              | 0                                                              | 0          |
|          | Injection site haemorrhage               | 7                                                                       | 9          | 12          | 160        | 169               | 0                                                              | 0          |
|          | Injection site hyperaesthesia            | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|          | Injection site hypersensitivity          | 4                                                                       | 4          | 97          | 216        | 220               | 0                                                              | 0          |
|          | Injection site hypertrophy               | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Injection site hypoaesthesia             | 8                                                                       | 21         | 2322        | 2493       | 2514              | 0                                                              | 0          |
|          | Injection site indentation               | 2                                                                       | 2          | 5           | 64         | 66                | 0                                                              | 0          |
|          | Injection site induration                | 18                                                                      | 31         | 842         | 4762       | 4793              | 0                                                              | 0          |
|          | Injection site inflammation              | 11                                                                      | 13         | 4184        | 9485       | 9498              | 0                                                              | 0          |
|          | Injection site injury                    | 0                                                                       | 0          | 1           | 15         | 15                | 0                                                              | 0          |
|          | Injection site irritation                | 1                                                                       | 2          | 7           | 164        | 166               | 0                                                              | 0          |
|          | Injection site joint discomfort          | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|          | Injection site joint erythema            | 2                                                                       | 3          | 15          | 21         | 24                | 0                                                              | 0          |
|          | Injection site joint inflammation        | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Injection site joint movement impairment | 1                                                                       | 2          | 16          | 34         | 36                | 0                                                              | 0          |
|          | Injection site joint pain                | 4                                                                       | 6          | 22          | 61         | 67                | 0                                                              | 0          |
|          | Injection site joint swelling            | 0                                                                       | 1          | 19          | 31         | 32                | 0                                                              | 0          |
|          | Injection site joint warmth              | 0                                                                       | 0          | 6           | 11         | 11                | 0                                                              | 0          |
|          | Injection site laceration                | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Injection site lymphadenopathy           | 3                                                                       | 5          | 38          | 75         | 80                | 0                                                              | 0          |
|          | Injection site macule                    | 0                                                                       | 0          | 5           | 14         | 14                | 0                                                              | 0          |
|          | Injection site mass                      | 82                                                                      | 101        | 93          | 1381       | 1482              | 0                                                              | 0          |
|          | Injection site movement impairment       | 7                                                                       | 9          | 39          | 92         | 101               | 0                                                              | 0          |

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|          |                                        | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                     | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Injection site muscle atrophy          | 2                                                                       | 2          | 1           | 1          | 3                 | 0                                                              | 0          |
|          | Injection site muscle weakness         | 0                                                                       | 3          | 11          | 38         | 41                | 0                                                              | 0          |
|          | Injection site necrosis                | 2                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Injection site nerve damage            | 0                                                                       | 0          | 0           | 3          | 3                 | 0                                                              | 0          |
|          | Injection site nodule                  | 5                                                                       | 8          | 9           | 451        | 459               | 0                                                              | 0          |
|          | Injection site oedema                  | 9                                                                       | 13         | 154         | 375        | 388               | 0                                                              | 0          |
|          | Injection site pain                    | 912                                                                     | 1143       | 16712       | 37609      | 38752             | 0                                                              | 0          |
|          | Injection site pallor                  | 0                                                                       | 0          | 2           | 12         | 12                | 0                                                              | 0          |
|          | Injection site panniculitis            | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Injection site papule                  | 0                                                                       | 0          | 9           | 42         | 42                | 0                                                              | 0          |
|          | Injection site paraesthesia            | 7                                                                       | 13         | 47          | 227        | 240               | 0                                                              | 0          |
|          | Injection site phlebitis               | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Injection site plaque                  | 3                                                                       | 4          | 4           | 11         | 15                | 0                                                              | 0          |
|          | Injection site pruritus                | 79                                                                      | 112        | 2539        | 15434      | 15546             | 0                                                              | 0          |
|          | Injection site rash                    | 82                                                                      | 118        | 426         | 6363       | 6481              | 0                                                              | 0          |
|          | Injection site reaction                | 535                                                                     | 678        | 1171        | 3665       | 4343              | 0                                                              | 0          |
|          | Injection site scab                    | 0                                                                       | 0          | 1           | 17         | 17                | 0                                                              | 0          |
|          | Injection site scar                    | 1                                                                       | 1          | 2           | 9          | 10                | 0                                                              | 0          |
|          | Injection site streaking               | 0                                                                       | 0          | 0           | 27         | 27                | 0                                                              | 0          |
|          | Injection site swelling                | 203                                                                     | 264        | 7296        | 21156      | 21420             | 0                                                              | 0          |
|          | Injection site telangiectasia          | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Injection site thrombosis              | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Injection site ulcer                   | 0                                                                       | 0          | 0           | 11         | 11                | 0                                                              | 0          |
|          | Injection site urticaria               | 14                                                                      | 19         | 130         | 988        | 1007              | 0                                                              | 0          |
|          | Injection site vasculitis              | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|          | Injection site vesicles                | 7                                                                       | 9          | 20          | 136        | 145               | 0                                                              | 0          |
|          | Injection site warmth                  | 74                                                                      | 101        | 4160        | 15175      | 15276             | 0                                                              | 0          |
|          | Injury associated with device          | 1                                                                       | 1          | 2           | 17         | 18                | 0                                                              | 0          |
|          | Instillation site erythema             | 0                                                                       | 0          | 2           | 2          | 2                 | 0                                                              | 0          |
|          | Instillation site induration           | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Instillation site paraesthesia         | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Instillation site warmth               | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|          | Irritability postvaccinal              | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|          | Local reaction                         | 17                                                                      | 22         | 417         | 759        | 781               | 0                                                              | 0          |
|          | Localised oedema                       | 29                                                                      | 44         | 57          | 96         | 140               | 0                                                              | 0          |
|          | Loss of control of legs                | 9                                                                       | 32         | 0           | 1          | 33                | 0                                                              | 0          |
|          | Macrosomia                             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Malaise                                | 2250                                                                    | 2969       | 19246       | 33336      | 36305             | 1                                                              | 1          |
|          | Mass                                   | 25                                                                      | 32         | 95          | 477        | 509               | 0                                                              | 0          |
|          | Medical device discomfort              | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Medical device pain                    | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Medical device site haemorrhage        | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Medical device site joint inflammation | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Medical device site joint pain         | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Medical device site phlebitis          | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Medical device site thrombosis         | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Metaplasia                             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Meteoropathy                           | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Moaning                                | 8                                                                       | 10         | 5           | 32         | 42                | 0                                                              | 0          |

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|          |                                          | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                       | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Mucosa vesicle                           | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|          | Mucosal discolouration                   | 0                                                                       | 0          | 0           | 3          | 3                 | 0                                                              | 0          |
|          | Mucosal disorder                         | 1                                                                       | 2          | 2           | 4          | 6                 | 0                                                              | 0          |
|          | Mucosal dryness                          | 0                                                                       | 2          | 3           | 9          | 11                | 0                                                              | 0          |
|          | Mucosal erosion                          | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Mucosal haemorrhage                      | 3                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Mucosal hypertrophy                      | 6                                                                       | 7          | 2           | 2          | 9                 | 0                                                              | 0          |
|          | Mucosal inflammation                     | 3                                                                       | 6          | 8           | 15         | 21                | 0                                                              | 0          |
|          | Mucosal pain                             | 0                                                                       | 1          | 0           | 2          | 3                 | 0                                                              | 0          |
|          | Mucosal ulceration                       | 2                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Multi-organ disorder                     | 2                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Multimorbidity                           | 4                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Multiple organ dysfunction syndrome      | 43                                                                      | 76         | 0           | 0          | 76                | 0                                                              | 0          |
|          | Necrosis                                 | 4                                                                       | 10         | 0           | 0          | 10                | 0                                                              | 0          |
|          | No adverse event                         | 1                                                                       | 1          | 196         | 1079       | 1080              | 0                                                              | 0          |
|          | No reaction on previous exposure to drug | 0                                                                       | 0          | 4           | 12         | 12                | 0                                                              | 0          |
|          | Nodule                                   | 18                                                                      | 30         | 69          | 455        | 485               | 0                                                              | 0          |
|          | Non-cardiac chest pain                   | 4                                                                       | 7          | 13          | 26         | 33                | 0                                                              | 0          |
|          | Non-pitting oedema                       | 0                                                                       | 0          | 1           | 4          | 4                 | 0                                                              | 0          |
|          | Nonspecific reaction                     | 0                                                                       | 0          | 1           | 14         | 14                | 0                                                              | 0          |
|          | Obstruction                              | 2                                                                       | 3          | 0           | 1          | 4                 | 0                                                              | 0          |
|          | Oedema                                   | 81                                                                      | 131        | 183         | 377        | 508               | 0                                                              | 0          |
|          | Oedema due to cardiac disease            | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Oedema mucosal                           | 2                                                                       | 2          | 9           | 11         | 13                | 0                                                              | 0          |
|          | Oedema peripheral                        | 180                                                                     | 266        | 263         | 651        | 917               | 0                                                              | 0          |
|          | Oral administration complication         | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Organ failure                            | 13                                                                      | 21         | 0           | 0          | 21                | 0                                                              | 0          |
|          | Pacemaker generated arrhythmia           | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Pain                                     | 2726                                                                    | 3716       | 5442        | 30241      | 33957             | 0                                                              | 0          |
|          | Papillitis                               | 2                                                                       | 2          | 0           | 1          | 3                 | 0                                                              | 0          |
|          | Paradoxical drug reaction                | 0                                                                       | 0          | 2           | 3          | 3                 | 0                                                              | 0          |
|          | Pelvic mass                              | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Perforation                              | 5                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Performance status decreased             | 4                                                                       | 5          | 20          | 24         | 29                | 0                                                              | 0          |
|          | Peripheral swelling                      | 1258                                                                    | 1743       | 2470        | 9139       | 10882             | 0                                                              | 0          |
|          | Physical deconditioning                  | 16                                                                      | 22         | 64          | 69         | 91                | 0                                                              | 0          |
|          | Pneumatoxis                              | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Polyp                                    | 1                                                                       | 2          | 2           | 3          | 5                 | 0                                                              | 0          |
|          | Polyserositis                            | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Positive dose response relationship      | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Potentiating drug interaction            | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|          | Pre-existing condition improved          | 0                                                                       | 0          | 7           | 31         | 31                | 0                                                              | 0          |
|          | Precancerous condition                   | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Premature ageing                         | 0                                                                       | 0          | 2           | 4          | 4                 | 0                                                              | 0          |
|          | Procedural failure                       | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Prosthetic cardiac valve thrombosis      | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Pseudoallergic reaction                  | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Pseudocyst                               | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Pseudohernia                             | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |

|          |                                                   | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|---------------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                                   | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                                | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Puncture site bruise                              | 3                                                                       | 4          | 3           | 3          | 7                 | 0                                                              | 0          |
|          | Puncture site erythema                            | 0                                                                       | 0          | 1           | 9          | 9                 | 0                                                              | 0          |
|          | Puncture site haemorrhage                         | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Puncture site induration                          | 0                                                                       | 0          | 7           | 11         | 11                | 0                                                              | 0          |
|          | Puncture site injury                              | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Puncture site oedema                              | 0                                                                       | 2          | 11          | 20         | 22                | 0                                                              | 0          |
|          | Puncture site pain                                | 3                                                                       | 3          | 38          | 57         | 60                | 0                                                              | 0          |
|          | Puncture site pruritus                            | 0                                                                       | 0          | 2           | 10         | 10                | 0                                                              | 0          |
|          | Puncture site reaction                            | 0                                                                       | 0          | 10          | 12         | 12                | 0                                                              | 0          |
|          | Puncture site swelling                            | 2                                                                       | 2          | 5           | 7          | 9                 | 0                                                              | 0          |
|          | Pyrexia                                           | 9029                                                                    | 11429      | 35268       | 77600      | 89029             | 1                                                              | 2          |
|          | Reactogenicity event                              | 0                                                                       | 0          | 7           | 7          | 7                 | 0                                                              | 0          |
|          | Rebound effect                                    | 0                                                                       | 1          | 2           | 2          | 3                 | 0                                                              | 0          |
|          | Retention cyst                                    | 1                                                                       | 1          | 1           | 2          | 3                 | 0                                                              | 0          |
|          | Scar inflammation                                 | 1                                                                       | 2          | 3           | 3          | 5                 | 0                                                              | 0          |
|          | Screaming                                         | 8                                                                       | 10         | 9           | 28         | 38                | 0                                                              | 0          |
|          | Secretion discharge                               | 22                                                                      | 28         | 45          | 144        | 172               | 0                                                              | 0          |
|          | Sensation of blood flow                           | 5                                                                       | 6          | 6           | 15         | 21                | 0                                                              | 0          |
|          | Sensation of foreign body                         | 21                                                                      | 47         | 56          | 348        | 395               | 0                                                              | 0          |
|          | Sense of oppression                               | 18                                                                      | 21         | 28          | 35         | 56                | 0                                                              | 0          |
|          | Sensitivity to weather change                     | 0                                                                       | 0          | 1           | 6          | 6                 | 0                                                              | 0          |
|          | Serositis                                         | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Shoulder injury related to vaccine administration | 24                                                                      | 34         | 16          | 65         | 99                | 0                                                              | 0          |
|          | Similar reaction on previous exposure to drug     | 1                                                                       | 2          | 0           | 9          | 11                | 0                                                              | 0          |
|          | Sluggishness                                      | 11                                                                      | 18         | 56          | 309        | 327               | 0                                                              | 0          |
|          | Soft tissue inflammation                          | 0                                                                       | 0          | 2           | 3          | 3                 | 0                                                              | 0          |
|          | Stenosis                                          | 4                                                                       | 5          | 4           | 7          | 12                | 0                                                              | 0          |
|          | Sudden cardiac death                              | 8                                                                       | 23         | 0           | 0          | 23                | 0                                                              | 0          |
|          | Sudden death                                      | 43                                                                      | 115        | 0           | 0          | 115               | 0                                                              | 0          |
|          | Suprapubic pain                                   | 0                                                                       | 1          | 2           | 6          | 7                 | 0                                                              | 0          |
|          | Surgical failure                                  | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Swelling                                          | 597                                                                     | 778        | 1857        | 6499       | 7277              | 0                                                              | 0          |
|          | Swelling face                                     | 209                                                                     | 381        | 516         | 2493       | 2874              | 0                                                              | 0          |
|          | Symptom masked                                    | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|          | Symptom recurrence                                | 8                                                                       | 8          | 9           | 39         | 47                | 0                                                              | 0          |
|          | Systemic inflammatory response syndrome           | 43                                                                      | 85         | 1           | 2          | 87                | 0                                                              | 0          |
|          | Temperature intolerance                           | 24                                                                      | 24         | 23          | 65         | 89                | 0                                                              | 0          |
|          | Temperature regulation disorder                   | 6                                                                       | 7          | 57          | 192        | 199               | 0                                                              | 0          |
|          | Tenderness                                        | 119                                                                     | 159        | 371         | 2267       | 2426              | 0                                                              | 0          |
|          | Terminal state                                    | 2                                                                       | 6          | 0           | 1          | 7                 | 0                                                              | 0          |
|          | Therapeutic product effect decreased              | 2                                                                       | 3          | 4           | 8          | 11                | 0                                                              | 0          |
|          | Therapeutic product effect delayed                | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Therapeutic product effect incomplete             | 0                                                                       | 0          | 0           | 3          | 3                 | 0                                                              | 0          |
|          | Therapeutic product effect increased              | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Therapeutic product ineffective                   | 1                                                                       | 1          | 4           | 9          | 10                | 0                                                              | 0          |
|          | Therapeutic response changed                      | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Therapeutic response decreased                    | 0                                                                       | 0          | 3           | 5          | 5                 | 0                                                              | 0          |
|          | Therapeutic response shortened                    | 0                                                                       | 0          | 1           | 7          | 7                 | 0                                                              | 0          |
|          | Therapeutic response unexpected                   | 1                                                                       | 1          | 177         | 345        | 346               | 0                                                              | 0          |

|          |                                            | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|--------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                            | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                         | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Therapy non-responder                      | 5                                                                       | 5          | 0           | 2          | 7                 | 0                                                              | 0          |
|          | Thirst                                     | 99                                                                      | 119        | 166         | 564        | 683               | 0                                                              | 0          |
|          | Thirst decreased                           | 1                                                                       | 2          | 5           | 22         | 24                | 0                                                              | 0          |
|          | Tissue discolouration                      | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Tissue infiltration                        | 2                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Tissue irritation                          | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Tissue rupture                             | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Treatment failure                          | 4                                                                       | 4          | 0           | 1          | 5                 | 0                                                              | 0          |
|          | Treatment noncompliance                    | 6                                                                       | 8          | 0           | 8          | 16                | 0                                                              | 0          |
|          | Ulcer                                      | 7                                                                       | 12         | 10          | 23         | 35                | 0                                                              | 0          |
|          | Ulcer haemorrhage                          | 5                                                                       | 11         | 0           | 0          | 11                | 0                                                              | 0          |
|          | Unevaluable event                          | 118                                                                     | 471        | 52          | 625        | 1096              | 0                                                              | 0          |
|          | Vaccination failure                        | 918                                                                     | 936        | 129         | 168        | 1104              | 0                                                              | 0          |
|          | Vaccination site anaesthesia               | 2                                                                       | 3          | 17          | 37         | 40                | 0                                                              | 0          |
|          | Vaccination site atrophy                   | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|          | Vaccination site bruising                  | 12                                                                      | 19         | 119         | 549        | 568               | 0                                                              | 0          |
|          | Vaccination site calcification             | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|          | Vaccination site coldness                  | 1                                                                       | 2          | 10          | 20         | 22                | 0                                                              | 0          |
|          | Vaccination site cyst                      | 0                                                                       | 0          | 2           | 3          | 3                 | 0                                                              | 0          |
|          | Vaccination site dermatitis                | 1                                                                       | 1          | 4           | 12         | 13                | 0                                                              | 0          |
|          | Vaccination site discharge                 | 0                                                                       | 1          | 12          | 59         | 60                | 0                                                              | 0          |
|          | Vaccination site discolouration            | 6                                                                       | 7          | 160         | 463        | 470               | 0                                                              | 0          |
|          | Vaccination site discomfort                | 3                                                                       | 4          | 374         | 615        | 619               | 0                                                              | 0          |
|          | Vaccination site dryness                   | 0                                                                       | 0          | 2           | 10         | 10                | 0                                                              | 0          |
|          | Vaccination site dysaesthesia              | 1                                                                       | 2          | 12          | 46         | 48                | 0                                                              | 0          |
|          | Vaccination site eczema                    | 1                                                                       | 1          | 17          | 30         | 31                | 0                                                              | 0          |
|          | Vaccination site erosion                   | 0                                                                       | 0          | 1           | 5          | 5                 | 0                                                              | 0          |
|          | Vaccination site erythema                  | 237                                                                     | 371        | 6138        | 15535      | 15906             | 0                                                              | 0          |
|          | Vaccination site exfoliation               | 1                                                                       | 1          | 1           | 10         | 11                | 0                                                              | 0          |
|          | Vaccination site extravasation             | 0                                                                       | 0          | 0           | 7          | 7                 | 0                                                              | 0          |
|          | Vaccination site fibrosis                  | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Vaccination site granuloma                 | 0                                                                       | 0          | 5           | 7          | 7                 | 0                                                              | 0          |
|          | Vaccination site haematoma                 | 9                                                                       | 12         | 94          | 178        | 190               | 0                                                              | 0          |
|          | Vaccination site haemorrhage               | 3                                                                       | 9          | 44          | 210        | 219               | 0                                                              | 0          |
|          | Vaccination site hyperaesthesia            | 4                                                                       | 4          | 8           | 10         | 14                | 0                                                              | 0          |
|          | Vaccination site hypersensitivity          | 0                                                                       | 0          | 25          | 61         | 61                | 0                                                              | 0          |
|          | Vaccination site hypertrophy               | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Vaccination site hypoaesthesia             | 5                                                                       | 9          | 45          | 79         | 88                | 0                                                              | 0          |
|          | Vaccination site induration                | 26                                                                      | 47         | 1422        | 3230       | 3277              | 0                                                              | 0          |
|          | Vaccination site inflammation              | 31                                                                      | 54         | 732         | 1729       | 1783              | 0                                                              | 0          |
|          | Vaccination site injury                    | 1                                                                       | 1          | 3           | 6          | 7                 | 0                                                              | 0          |
|          | Vaccination site irritation                | 2                                                                       | 2          | 25          | 89         | 91                | 0                                                              | 0          |
|          | Vaccination site joint discomfort          | 0                                                                       | 0          | 3           | 5          | 5                 | 0                                                              | 0          |
|          | Vaccination site joint effusion            | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Vaccination site joint erythema            | 5                                                                       | 7          | 38          | 150        | 157               | 0                                                              | 0          |
|          | Vaccination site joint inflammation        | 1                                                                       | 1          | 5           | 9          | 10                | 0                                                              | 0          |
|          | Vaccination site joint movement impairment | 3                                                                       | 6          | 24          | 45         | 51                | 0                                                              | 0          |
|          | Vaccination site joint pain                | 6                                                                       | 7          | 59          | 82         | 89                | 0                                                              | 0          |
|          | Vaccination site joint swelling            | 5                                                                       | 6          | 45          | 78         | 84                | 0                                                              | 0          |

|                         |                                            | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|-------------------------|--------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|                         |                                            | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM                | PT                                         | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|                         | Vaccination site joint warmth              | 1                                                                       | 1          | 7           | 12         | 13                | 0                                                              | 0          |
|                         | Vaccination site laceration                | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|                         | Vaccination site lymphadenopathy           | 17                                                                      | 30         | 291         | 615        | 645               | 0                                                              | 0          |
|                         | Vaccination site macule                    | 6                                                                       | 6          | 9           | 20         | 26                | 0                                                              | 0          |
|                         | Vaccination site mass                      | 29                                                                      | 39         | 288         | 1191       | 1230              | 0                                                              | 0          |
|                         | Vaccination site movement impairment       | 43                                                                      | 57         | 387         | 701        | 758               | 0                                                              | 0          |
|                         | Vaccination site necrosis                  | 2                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|                         | Vaccination site nerve damage              | 1                                                                       | 1          | 1           | 3          | 4                 | 0                                                              | 0          |
|                         | Vaccination site nodule                    | 1                                                                       | 3          | 19          | 139        | 142               | 0                                                              | 0          |
|                         | Vaccination site oedema                    | 54                                                                      | 94         | 369         | 667        | 761               | 0                                                              | 0          |
|                         | Vaccination site pain                      | 557                                                                     | 802        | 15454       | 28686      | 29488             | 0                                                              | 0          |
|                         | Vaccination site pallor                    | 0                                                                       | 0          | 2           | 4          | 4                 | 0                                                              | 0          |
|                         | Vaccination site papule                    | 2                                                                       | 3          | 7           | 34         | 37                | 0                                                              | 0          |
|                         | Vaccination site paraesthesia              | 7                                                                       | 11         | 76          | 151        | 162               | 0                                                              | 0          |
|                         | Vaccination site phlebitis                 | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|                         | Vaccination site photosensitivity reaction | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|                         | Vaccination site plaque                    | 1                                                                       | 4          | 36          | 65         | 69                | 0                                                              | 0          |
|                         | Vaccination site pruritus                  | 87                                                                      | 152        | 3254        | 9258       | 9410              | 0                                                              | 0          |
|                         | Vaccination site rash                      | 57                                                                      | 102        | 1046        | 4303       | 4405              | 0                                                              | 0          |
|                         | Vaccination site reaction                  | 77                                                                      | 140        | 3349        | 5121       | 5261              | 0                                                              | 0          |
|                         | Vaccination site recall reaction           | 1                                                                       | 1          | 5           | 6          | 7                 | 0                                                              | 0          |
|                         | Vaccination site scab                      | 0                                                                       | 0          | 7           | 25         | 25                | 0                                                              | 0          |
|                         | Vaccination site scar                      | 2                                                                       | 2          | 8           | 33         | 35                | 0                                                              | 0          |
|                         | Vaccination site streaking                 | 0                                                                       | 2          | 2           | 17         | 19                | 0                                                              | 0          |
|                         | Vaccination site swelling                  | 208                                                                     | 298        | 6508        | 13117      | 13415             | 0                                                              | 0          |
|                         | Vaccination site thrombosis                | 0                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|                         | Vaccination site ulcer                     | 0                                                                       | 0          | 1           | 3          | 3                 | 0                                                              | 0          |
|                         | Vaccination site urticaria                 | 13                                                                      | 19         | 133         | 680        | 699               | 0                                                              | 0          |
|                         | Vaccination site vasculitis                | 1                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|                         | Vaccination site vesicles                  | 4                                                                       | 4          | 38          | 109        | 113               | 0                                                              | 0          |
|                         | Vaccination site warmth                    | 91                                                                      | 148        | 3623        | 8228       | 8376              | 0                                                              | 0          |
|                         | Vaccine positive rechallenge               | 9                                                                       | 10         | 7           | 242        | 252               | 0                                                              | 0          |
|                         | Vascular stent thrombosis                  | 1                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|                         | Vessel puncture site bruise                | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|                         | Vessel puncture site erythema              | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|                         | Vessel puncture site haematoma             | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                         | Vessel puncture site inflammation          | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|                         | Vessel puncture site swelling              | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|                         | Visceral pain                              | 2                                                                       | 3          | 1           | 6          | 9                 | 0                                                              | 0          |
|                         | Withdrawal syndrome                        | 6                                                                       | 7          | 3           | 6          | 13                | 0                                                              | 0          |
|                         | Xerosis                                    | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
| Hepatobiliary disorders | *** SOC TOTAL ***                          | 499                                                                     | 831        | 123         | 212        | 1043              | 0                                                              | 0          |
|                         | Acute fatty liver of pregnancy             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                         | Acute hepatic failure                      | 9                                                                       | 17         | 0           | 0          | 17                | 0                                                              | 0          |
|                         | Alcoholic liver disease                    | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                         | Autoimmune cholangitis                     | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                         | Autoimmune hepatitis                       | 34                                                                      | 45         | 2           | 2          | 47                | 0                                                              | 0          |
|                         | Bile duct stenosis                         | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                         | Bile duct stone                            | 2                                                                       | 4          | 0           | 1          | 5                 | 0                                                              | 0          |

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|----------|----------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                  | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                               | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Biliary colic                    | 8                                                                       | 11         | 8           | 18         | 29                | 0                                                              | 0          |
|          | Biliary dilatation               | 1                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Biliary dyskinesia               | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Biliary obstruction              | 4                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Biliary tract disorder           | 2                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Budd-Chiari syndrome             | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Cholangitis                      | 8                                                                       | 10         | 0           | 1          | 11                | 0                                                              | 0          |
|          | Cholangitis acute                | 0                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Cholecystitis                    | 12                                                                      | 33         | 0           | 0          | 33                | 0                                                              | 0          |
|          | Cholecystitis acute              | 14                                                                      | 24         | 0           | 0          | 24                | 0                                                              | 0          |
|          | Cholelithiasis                   | 29                                                                      | 53         | 5           | 18         | 71                | 0                                                              | 0          |
|          | Cholestasis                      | 7                                                                       | 8          | 0           | 0          | 8                 | 0                                                              | 0          |
|          | Cholestasis of pregnancy         | 3                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Cholestatic liver injury         | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Chronic hepatic failure          | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Chronic hepatitis                | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Cirrhosis alcoholic              | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Congestive hepatopathy           | 3                                                                       | 6          | 0           | 0          | 6                 | 0                                                              | 0          |
|          | Drug-induced liver injury        | 6                                                                       | 10         | 0           | 0          | 10                | 0                                                              | 0          |
|          | Gallbladder disorder             | 10                                                                      | 21         | 3           | 12         | 33                | 0                                                              | 0          |
|          | Gallbladder enlargement          | 10                                                                      | 14         | 0           | 0          | 14                | 0                                                              | 0          |
|          | Gallbladder hypofunction         | 1                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Gallbladder necrosis             | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Gallbladder oedema               | 2                                                                       | 5          | 1           | 1          | 6                 | 0                                                              | 0          |
|          | Gallbladder polyp                | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Gallbladder rupture              | 3                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Granulomatous liver disease      | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Haemobilia                       | 0                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Hepatic artery thrombosis        | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Hepatic atrophy                  | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Hepatic cirrhosis                | 16                                                                      | 24         | 0           | 1          | 25                | 0                                                              | 0          |
|          | Hepatic cyst                     | 5                                                                       | 7          | 0           | 1          | 8                 | 0                                                              | 0          |
|          | Hepatic cytolysis                | 15                                                                      | 22         | 0           | 0          | 22                | 0                                                              | 0          |
|          | Hepatic failure                  | 16                                                                      | 33         | 0           | 0          | 33                | 0                                                              | 0          |
|          | Hepatic fibrosis                 | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Hepatic function abnormal        | 20                                                                      | 25         | 11          | 13         | 38                | 0                                                              | 0          |
|          | Hepatic haematoma                | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Hepatic infarction               | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Hepatic ischaemia                | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Hepatic lesion                   | 8                                                                       | 12         | 3           | 5          | 17                | 0                                                              | 0          |
|          | Hepatic lymphocytic infiltration | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Hepatic mass                     | 1                                                                       | 5          | 0           | 3          | 8                 | 0                                                              | 0          |
|          | Hepatic necrosis                 | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Hepatic pain                     | 13                                                                      | 17         | 23          | 40         | 57                | 0                                                              | 0          |
|          | Hepatic perfusion disorder       | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Hepatic steatosis                | 12                                                                      | 22         | 8           | 11         | 33                | 0                                                              | 0          |
|          | Hepatic vascular thrombosis      | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Hepatic vein thrombosis          | 4                                                                       | 8          | 0           | 0          | 8                 | 0                                                              | 0          |
|          | Hepatitis                        | 26                                                                      | 44         | 2           | 3          | 47                | 0                                                              | 0          |

|                         |                                         | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|-------------------------|-----------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|                         |                                         | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM                | PT                                      | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|                         | Hepatitis acute                         | 15                                                                      | 21         | 0           | 0          | 21                | 0                                                              | 0          |
|                         | Hepatitis cholestatic                   | 1                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|                         | Hepatitis fulminant                     | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                         | Hepatitis toxic                         | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                         | Hepatocellular injury                   | 7                                                                       | 11         | 0           | 0          | 11                | 0                                                              | 0          |
|                         | Hepatomegaly                            | 9                                                                       | 17         | 10          | 16         | 33                | 0                                                              | 0          |
|                         | Hepatorenal syndrome                    | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                         | Hepatosplenomegaly                      | 4                                                                       | 7          | 0           | 0          | 7                 | 0                                                              | 0          |
|                         | Hepatotoxicity                          | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|                         | Hydrocholecystis                        | 1                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|                         | Hyperbilirubinaemia                     | 5                                                                       | 10         | 1           | 1          | 11                | 0                                                              | 0          |
|                         | Hyperbilirubinaemia neonatal            | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                         | Hypertransaminasaemia                   | 5                                                                       | 6          | 3           | 3          | 9                 | 0                                                              | 0          |
|                         | Immune-mediated hepatic disorder        | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                         | Immune-mediated hepatitis               | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                         | Ischaemic hepatitis                     | 4                                                                       | 8          | 0           | 0          | 8                 | 0                                                              | 0          |
|                         | Jaundice                                | 23                                                                      | 46         | 14          | 26         | 72                | 0                                                              | 0          |
|                         | Jaundice cholestatic                    | 4                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|                         | Liver disorder                          | 20                                                                      | 34         | 22          | 26         | 60                | 0                                                              | 0          |
|                         | Liver injury                            | 18                                                                      | 28         | 0           | 0          | 28                | 0                                                              | 0          |
|                         | Liver tenderness                        | 1                                                                       | 2          | 2           | 3          | 5                 | 0                                                              | 0          |
|                         | Mixed liver injury                      | 3                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|                         | Non-alcoholic steatohepatitis           | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                         | Nonalcoholic fatty liver disease        | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                         | Ocular icterus                          | 3                                                                       | 5          | 4           | 6          | 11                | 0                                                              | 0          |
|                         | Perforation bile duct                   | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                         | Perihepatic discomfort                  | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|                         | Periportal oedema                       | 3                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|                         | Pneumobilia                             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                         | Portal fibrosis                         | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                         | Portal hypertension                     | 1                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|                         | Portal shunt                            | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                         | Portal vein embolism                    | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                         | Portal vein occlusion                   | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                         | Portal vein thrombosis                  | 28                                                                      | 46         | 0           | 0          | 46                | 0                                                              | 0          |
|                         | Portosplenomesenteric venous thrombosis | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                         | Primary biliary cholangitis             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                         | Venoocclusive liver disease             | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
| Immune system disorders | *** SOC TOTAL ***                       | 1662                                                                    | 2910       | 2190        | 4041       | 6951              | 0                                                              | 0          |
|                         | Allergic oedema                         | 2                                                                       | 3          | 2           | 6          | 9                 | 0                                                              | 0          |
|                         | Allergic reaction to excipient          | 0                                                                       | 0          | 2           | 3          | 3                 | 0                                                              | 0          |
|                         | Allergy to animal                       | 0                                                                       | 1          | 4           | 5          | 6                 | 0                                                              | 0          |
|                         | Allergy to arthropod bite               | 0                                                                       | 0          | 4           | 6          | 6                 | 0                                                              | 0          |
|                         | Allergy to arthropod sting              | 4                                                                       | 4          | 3           | 4          | 8                 | 0                                                              | 0          |
|                         | Allergy to chemicals                    | 2                                                                       | 2          | 1           | 7          | 9                 | 0                                                              | 0          |
|                         | Allergy to metals                       | 1                                                                       | 1          | 5           | 6          | 7                 | 0                                                              | 0          |
|                         | Allergy to plants                       | 0                                                                       | 0          | 0           | 3          | 3                 | 0                                                              | 0          |
|                         | Allergy to surgical sutures             | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|                         | Allergy to vaccine                      | 17                                                                      | 41         | 115         | 296        | 337               | 0                                                              | 0          |



|          |                                                 | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|-------------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                                 | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                              | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Allergy to venom                                | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Amyloidosis                                     | 5                                                                       | 7          | 0           | 0          | 7                 | 0                                                              | 0          |
|          | Anamnestic reaction                             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Anaphylactic reaction                           | 740                                                                     | 1452       | 9           | 19         | 1471              | 0                                                              | 0          |
|          | Anaphylactic shock                              | 83                                                                      | 177        | 0           | 1          | 178               | 0                                                              | 0          |
|          | Anaphylactoid reaction                          | 43                                                                      | 63         | 0           | 2          | 65                | 0                                                              | 0          |
|          | Anaphylactoid shock                             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Anti-neutrophil cytoplasmic antibody positivity | 5                                                                       | 7          | 0           | 0          | 7                 | 0                                                              | 0          |
|          | Atopy                                           | 0                                                                       | 0          | 3           | 4          | 4                 | 0                                                              | 0          |
|          | Autoimmune disorder                             | 72                                                                      | 136        | 7           | 15         | 151               | 0                                                              | 0          |
|          | Autoinflammatory disease                        | 2                                                                       | 3          | 1           | 2          | 5                 | 0                                                              | 0          |
|          | Bacille Calmette-Guerin scar reactivation       | 14                                                                      | 18         | 46          | 64         | 82                | 0                                                              | 0          |
|          | Caffeine allergy                                | 1                                                                       | 1          | 1           | 2          | 3                 | 0                                                              | 0          |
|          | Cell-mediated immune deficiency                 | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Chronic allograft nephropathy                   | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Chronic graft versus host disease               | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Contrast media allergy                          | 2                                                                       | 3          | 0           | 2          | 5                 | 0                                                              | 0          |
|          | Contrast media reaction                         | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Corneal graft rejection                         | 8                                                                       | 9          | 0           | 0          | 9                 | 0                                                              | 0          |
|          | Cross sensitivity reaction                      | 0                                                                       | 0          | 2           | 2          | 2                 | 0                                                              | 0          |
|          | Cytokine release syndrome                       | 1                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Cytokine storm                                  | 6                                                                       | 17         | 0           | 0          | 17                | 0                                                              | 0          |
|          | Decreased immune responsiveness                 | 2                                                                       | 3          | 8           | 16         | 19                | 0                                                              | 0          |
|          | Drug hypersensitivity                           | 20                                                                      | 27         | 19          | 51         | 78                | 0                                                              | 0          |
|          | Dust allergy                                    | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Eosinophilic granulomatosis with polyangiitis   | 3                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Food allergy                                    | 11                                                                      | 13         | 14          | 28         | 41                | 0                                                              | 0          |
|          | Graft versus host disease                       | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Haemophagocytic lymphohistiocytosis             | 11                                                                      | 26         | 0           | 0          | 26                | 0                                                              | 0          |
|          | Hypersensitivity                                | 423                                                                     | 631        | 868         | 2133       | 2764              | 0                                                              | 0          |
|          | Hypogammaglobulinaemia                          | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Immune reconstitution inflammatory syndrome     | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Immune system disorder                          | 21                                                                      | 26         | 31          | 73         | 99                | 0                                                              | 0          |
|          | Immune-mediated adverse reaction                | 7                                                                       | 9          | 4           | 12         | 21                | 0                                                              | 0          |
|          | Immunisation reaction                           | 35                                                                      | 36         | 890         | 908        | 944               | 0                                                              | 0          |
|          | Immunodeficiency                                | 19                                                                      | 30         | 3           | 4          | 34                | 0                                                              | 0          |
|          | Immunodeficiency common variable                | 0                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Immunosuppression                               | 11                                                                      | 16         | 0           | 0          | 16                | 0                                                              | 0          |
|          | Infusion related hypersensitivity reaction      | 1                                                                       | 1          | 7           | 13         | 14                | 0                                                              | 0          |
|          | Iodine allergy                                  | 0                                                                       | 0          | 1           | 3          | 3                 | 0                                                              | 0          |
|          | Kidney transplant rejection                     | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Liver transplant rejection                      | 0                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Loefgren syndrome                               | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Lung transplant rejection                       | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Milk allergy                                    | 2                                                                       | 2          | 1           | 1          | 3                 | 0                                                              | 0          |
|          | Mite allergy                                    | 2                                                                       | 2          | 3           | 3          | 5                 | 0                                                              | 0          |
|          | Multiple allergies                              | 3                                                                       | 3          | 3           | 12         | 15                | 0                                                              | 0          |
|          | Multisystem inflammatory syndrome               | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Multisystem inflammatory syndrome in adults     | 5                                                                       | 5          | 1           | 1          | 6                 | 0                                                              | 0          |

|                             |                                           | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|-----------------------------|-------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|                             |                                           | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM                    | PT                                        | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|                             | Multisystem inflammatory syndrome in chil | 4                                                                       | 6          | 0           | 0          | 6                 | 0                                                              | 0          |
|                             | Overlap syndrome                          | 0                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|                             | Perfume sensitivity                       | 1                                                                       | 1          | 1           | 2          | 3                 | 0                                                              | 0          |
|                             | Polymers allergy                          | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|                             | Reaction to excipient                     | 1                                                                       | 1          | 1           | 4          | 5                 | 0                                                              | 0          |
|                             | Reaction to food additive                 | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|                             | Reaction to preservatives                 | 1                                                                       | 2          | 2           | 15         | 17                | 0                                                              | 0          |
|                             | Rubber sensitivity                        | 0                                                                       | 0          | 1           | 4          | 4                 | 0                                                              | 0          |
|                             | Sarcoidosis                               | 9                                                                       | 15         | 1           | 1          | 16                | 0                                                              | 0          |
|                             | Seasonal allergy                          | 9                                                                       | 13         | 44          | 79         | 92                | 0                                                              | 0          |
|                             | Sensitisation                             | 1                                                                       | 4          | 8           | 16         | 20                | 0                                                              | 0          |
|                             | Serum sickness                            | 3                                                                       | 4          | 4           | 12         | 16                | 0                                                              | 0          |
|                             | Serum sickness-like reaction              | 0                                                                       | 1          | 1           | 4          | 5                 | 0                                                              | 0          |
|                             | Sunscreen sensitivity                     | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|                             | Systemic immune activation                | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                             | Transplant rejection                      | 4                                                                       | 6          | 0           | 0          | 6                 | 0                                                              | 0          |
|                             | Type I hypersensitivity                   | 18                                                                      | 24         | 3           | 3          | 27                | 0                                                              | 0          |
|                             | Type II hypersensitivity                  | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                             | Type III immune complex mediated reaction | 3                                                                       | 13         | 0           | 3          | 16                | 0                                                              | 0          |
|                             | Type IV hypersensitivity reaction         | 4                                                                       | 8          | 64          | 183        | 191               | 0                                                              | 0          |
|                             | Vaccine associated enhanced disease       | 3                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
| Infections and infestations | *** SOC TOTAL ***                         | 10285                                                                   | 14809      | 10387       | 19361      | 34170             | 1                                                              | 1          |
|                             | Abdominal abscess                         | 5                                                                       | 7          | 0           | 0          | 7                 | 0                                                              | 0          |
|                             | Abdominal infection                       | 6                                                                       | 10         | 0           | 0          | 10                | 0                                                              | 0          |
|                             | Abdominal wall abscess                    | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                             | Abortion infected                         | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                             | Abscess                                   | 16                                                                      | 21         | 14          | 39         | 60                | 0                                                              | 0          |
|                             | Abscess intestinal                        | 1                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|                             | Abscess jaw                               | 0                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|                             | Abscess limb                              | 8                                                                       | 10         | 2           | 9          | 19                | 0                                                              | 0          |
|                             | Abscess neck                              | 2                                                                       | 3          | 0           | 2          | 5                 | 0                                                              | 0          |
|                             | Abscess of eyelid                         | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|                             | Abscess oral                              | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|                             | Abscess rupture                           | 0                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                             | Acarodermatitis                           | 1                                                                       | 1          | 1           | 3          | 4                 | 0                                                              | 0          |
|                             | Acid fast bacilli infection               | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                             | Acinetobacter bacteraemia                 | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                             | Acne pustular                             | 1                                                                       | 1          | 4           | 5          | 6                 | 0                                                              | 0          |
|                             | Acute hepatitis B                         | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|                             | Acute sinusitis                           | 1                                                                       | 2          | 4           | 10         | 12                | 0                                                              | 0          |
|                             | Adenoviral meningitis                     | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                             | Adenovirus infection                      | 0                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|                             | Administration site abscess               | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|                             | Administration site cellulitis            | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|                             | Aerococcus urinae infection               | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                             | Amniotic cavity infection                 | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                             | Anal abscess                              | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|                             | Anal fungal infection                     | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|                             | Appendiceal abscess                       | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |

|          |                                         | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|-----------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                         | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                      | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Appendicitis                            | 116                                                                     | 238        | 3           | 3          | 241               | 0                                                              | 0          |
|          | Appendicitis perforated                 | 13                                                                      | 29         | 0           | 0          | 29                | 0                                                              | 0          |
|          | Application site cellulitis             | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Application site infection              | 2                                                                       | 2          | 0           | 1          | 3                 | 0                                                              | 0          |
|          | Application site pustules               | 0                                                                       | 0          | 4           | 5          | 5                 | 0                                                              | 0          |
|          | Arthritis bacterial                     | 4                                                                       | 9          | 0           | 0          | 9                 | 0                                                              | 0          |
|          | Arthritis infective                     | 1                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Arthropod-borne disease                 | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Aspergillus infection                   | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Asymptomatic COVID-19                   | 93                                                                      | 103        | 101         | 146        | 249               | 0                                                              | 0          |
|          | Asymptomatic bacteriuria                | 2                                                                       | 3          | 0           | 1          | 4                 | 0                                                              | 0          |
|          | Atypical pneumonia                      | 21                                                                      | 42         | 1           | 1          | 43                | 0                                                              | 0          |
|          | BK virus infection                      | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Babesiosis                              | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Bacteraemia                             | 15                                                                      | 25         | 1           | 1          | 26                | 0                                                              | 0          |
|          | Bacterial abdominal infection           | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Bacterial disease carrier               | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Bacterial infection                     | 17                                                                      | 27         | 11          | 30         | 57                | 0                                                              | 0          |
|          | Bacterial prostatitis                   | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Bacterial sepsis                        | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Bacterial vaginosis                     | 1                                                                       | 1          | 1           | 5          | 6                 | 0                                                              | 0          |
|          | Bacteriuria                             | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Bacteroides bacteraemia                 | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Bartholinitis                           | 0                                                                       | 0          | 2           | 2          | 2                 | 0                                                              | 0          |
|          | Beta haemolytic streptococcal infection | 4                                                                       | 8          | 0           | 0          | 8                 | 0                                                              | 0          |
|          | Biliary sepsis                          | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Biliary tract infection                 | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Blastomycosis                           | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Blister infected                        | 0                                                                       | 0          | 0           | 3          | 3                 | 0                                                              | 0          |
|          | Body tinea                              | 0                                                                       | 1          | 4           | 5          | 6                 | 0                                                              | 0          |
|          | Bone tuberculosis                       | 1                                                                       | 2          | 0           | 1          | 3                 | 0                                                              | 0          |
|          | Borrelia infection                      | 4                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Brain abscess                           | 1                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Breast abscess                          | 0                                                                       | 0          | 3           | 4          | 4                 | 0                                                              | 0          |
|          | Breast cellulitis                       | 1                                                                       | 2          | 0           | 1          | 3                 | 0                                                              | 0          |
|          | Bronchiolitis                           | 2                                                                       | 7          | 0           | 0          | 7                 | 0                                                              | 0          |
|          | Bronchitis                              | 41                                                                      | 68         | 65          | 143        | 211               | 0                                                              | 0          |
|          | Bronchitis bacterial                    | 0                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Bronchitis viral                        | 0                                                                       | 0          | 2           | 2          | 2                 | 0                                                              | 0          |
|          | Bronchopulmonary aspergillosis          | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Bronchopulmonary aspergillosis allergic | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Bullous erysipelas                      | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | COVID-19                                | 4274                                                                    | 4987       | 3512        | 5928       | 10915             | 0                                                              | 0          |
|          | COVID-19 pneumonia                      | 643                                                                     | 846        | 3           | 4          | 850               | 0                                                              | 0          |
|          | Campylobacter colitis                   | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Campylobacter gastroenteritis           | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Campylobacter infection                 | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Candida infection                       | 9                                                                       | 11         | 10          | 40         | 51                | 0                                                              | 0          |
|          | Carbuncle                               | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |

|          |                                             | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|---------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                             | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                          | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Cardiac infection                           | 5                                                                       | 6          | 0           | 0          | 6                 | 0                                                              | 0          |
|          | Cardiac valve vegetation                    | 2                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Cat scratch disease                         | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Cavernous sinus thrombosis                  | 4                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Cellulitis                                  | 220                                                                     | 1085       | 32          | 92         | 1177              | 0                                                              | 0          |
|          | Cellulitis orbital                          | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Cellulitis staphylococcal                   | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Central nervous system infection            | 0                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Central nervous system viral infection      | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Cervicitis                                  | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Chest wall abscess                          | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Chikungunya virus infection                 | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Chlamydial infection                        | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Cholangitis infective                       | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Cholecystitis infective                     | 5                                                                       | 11         | 0           | 0          | 11                | 0                                                              | 0          |
|          | Chorioretinitis                             | 1                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Chronic active Epstein-Barr virus infection | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Chronic hepatitis C                         | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Chronic sinusitis                           | 4                                                                       | 6          | 1           | 2          | 8                 | 0                                                              | 0          |
|          | Clostridial infection                       | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Clostridium difficile colitis               | 9                                                                       | 26         | 0           | 0          | 26                | 0                                                              | 0          |
|          | Clostridium difficile infection             | 13                                                                      | 20         | 0           | 0          | 20                | 0                                                              | 0          |
|          | Coccidioidomycosis                          | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Coinfection                                 | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Colonic abscess                             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Colostomy infection                         | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Community acquired infection                | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Complicated appendicitis                    | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Conjunctivitis                              | 16                                                                      | 27         | 49          | 108        | 135               | 0                                                              | 0          |
|          | Conjunctivitis bacterial                    | 2                                                                       | 3          | 1           | 1          | 4                 | 0                                                              | 0          |
|          | Conjunctivitis viral                        | 1                                                                       | 1          | 1           | 2          | 3                 | 0                                                              | 0          |
|          | Corneal infection                           | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Coronavirus infection                       | 5                                                                       | 5          | 3           | 8          | 13                | 0                                                              | 0          |
|          | Coronavirus pneumonia                       | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Coxsackie viral infection                   | 0                                                                       | 0          | 2           | 2          | 2                 | 0                                                              | 0          |
|          | Cranial nerve infection                     | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Creutzfeldt-Jakob disease                   | 5                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Croup infectious                            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Cutaneous mucormycosis                      | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Cystitis                                    | 28                                                                      | 40         | 49          | 101        | 141               | 0                                                              | 0          |
|          | Cystitis viral                              | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Cytomegalovirus hepatitis                   | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Cytomegalovirus infection                   | 6                                                                       | 7          | 2           | 3          | 10                | 0                                                              | 0          |
|          | Cytomegalovirus infection reactivation      | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Cytomegalovirus viraemia                    | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Dacryocanaliculitis                         | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Dacryocystitis                              | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Dengue fever                                | 2                                                                       | 2          | 1           | 1          | 3                 | 0                                                              | 0          |
|          | Dermatitis infected                         | 1                                                                       | 1          | 1           | 4          | 5                 | 0                                                              | 0          |

|          |                                              | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|----------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                              | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                           | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Dermatophytosis                              | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Dermo-hypodermatitis                         | 9                                                                       | 15         | 1           | 1          | 16                | 0                                                              | 0          |
|          | Device related bacteraemia                   | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Device related infection                     | 4                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Diabetic foot infection                      | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Diarrhoea infectious                         | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Disseminated mycobacterium avium compl       | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Disseminated tuberculosis                    | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Disseminated varicella zoster virus infectio | 1                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Diverticulitis                               | 40                                                                      | 89         | 3           | 7          | 96                | 0                                                              | 0          |
|          | Diverticulitis intestinal perforated         | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Dysentery                                    | 17                                                                      | 30         | 11          | 14         | 44                | 0                                                              | 0          |
|          | Ear infection                                | 13                                                                      | 23         | 62          | 133        | 156               | 0                                                              | 0          |
|          | Ear infection bacterial                      | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Ear infection viral                          | 1                                                                       | 1          | 0           | 2          | 3                 | 0                                                              | 0          |
|          | Eczema herpeticum                            | 8                                                                       | 8          | 0           | 0          | 8                 | 0                                                              | 0          |
|          | Eczema impetiginous                          | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Eczema infected                              | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Embolic pneumonia                            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Empyema                                      | 6                                                                       | 6          | 0           | 0          | 6                 | 0                                                              | 0          |
|          | Encephalitis                                 | 50                                                                      | 76         | 1           | 1          | 77                | 1                                                              | 1          |
|          | Encephalitis Japanese B                      | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Encephalitis brain stem                      | 0                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Encephalitis viral                           | 1                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Encephalomyelitis                            | 7                                                                       | 11         | 0           | 0          | 11                | 0                                                              | 0          |
|          | Endocarditis                                 | 11                                                                      | 17         | 0           | 0          | 17                | 0                                                              | 0          |
|          | Endocarditis bacterial                       | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Endocarditis staphylococcal                  | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Endometritis                                 | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Endophthalmitis                              | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Enteritis infectious                         | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Enterobacter infection                       | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Enterobiasis                                 | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Enterococcal bacteraemia                     | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Enterococcal infection                       | 1                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Enterocolitis infectious                     | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Enterovirus infection                        | 0                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Epidemic polyarthritis                       | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Epididymitis                                 | 15                                                                      | 23         | 2           | 2          | 25                | 0                                                              | 0          |
|          | Epiglottitis                                 | 3                                                                       | 8          | 0           | 0          | 8                 | 0                                                              | 0          |
|          | Epiglottitis obstructive                     | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Epstein-Barr viraemia                        | 1                                                                       | 3          | 0           | 1          | 4                 | 0                                                              | 0          |
|          | Epstein-Barr virus infection                 | 7                                                                       | 7          | 7           | 12         | 19                | 0                                                              | 0          |
|          | Epstein-Barr virus infection reactivation    | 12                                                                      | 17         | 2           | 3          | 20                | 0                                                              | 0          |
|          | Erysipelas                                   | 93                                                                      | 169        | 19          | 23         | 192               | 0                                                              | 0          |
|          | Erysipeloid                                  | 0                                                                       | 0          | 2           | 2          | 2                 | 0                                                              | 0          |
|          | Erythema induratum                           | 5                                                                       | 11         | 0           | 1          | 12                | 0                                                              | 0          |
|          | Erythema infectiosum                         | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Erythema migrans                             | 0                                                                       | 0          | 4           | 12         | 12                | 0                                                              | 0          |

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|----------|---------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                       | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                    | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Erythrasma                            | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Escherichia bacteraemia               | 7                                                                       | 10         | 0           | 0          | 10                | 0                                                              | 0          |
|          | Escherichia infection                 | 9                                                                       | 13         | 0           | 0          | 13                | 0                                                              | 0          |
|          | Escherichia pyelonephritis            | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Escherichia sepsis                    | 0                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Escherichia urinary tract infection   | 5                                                                       | 7          | 0           | 0          | 7                 | 0                                                              | 0          |
|          | Extradural abscess                    | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Eye abscess                           | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Eye infection                         | 10                                                                      | 13         | 9           | 39         | 52                | 0                                                              | 0          |
|          | Eye infection bacterial               | 2                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Eye infection viral                   | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Eyelid boil                           | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Eyelid infection                      | 1                                                                       | 1          | 6           | 9          | 10                | 0                                                              | 0          |
|          | Febrile infection                     | 2                                                                       | 2          | 2           | 2          | 4                 | 0                                                              | 0          |
|          | Folliculitis                          | 1                                                                       | 1          | 9           | 21         | 22                | 0                                                              | 0          |
|          | Fournier's gangrene                   | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Fungaemia                             | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Fungal infection                      | 6                                                                       | 9          | 19          | 52         | 61                | 0                                                              | 0          |
|          | Fungal skin infection                 | 2                                                                       | 4          | 8           | 16         | 20                | 0                                                              | 0          |
|          | Furuncle                              | 9                                                                       | 10         | 12          | 33         | 43                | 0                                                              | 0          |
|          | Gangrene                              | 5                                                                       | 7          | 0           | 1          | 8                 | 0                                                              | 0          |
|          | Gastric infection                     | 1                                                                       | 2          | 2           | 2          | 4                 | 0                                                              | 0          |
|          | Gastroenteritis                       | 19                                                                      | 24         | 11          | 18         | 42                | 0                                                              | 0          |
|          | Gastroenteritis Escherichia coli      | 2                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Gastroenteritis norovirus             | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Gastroenteritis rotavirus             | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Gastroenteritis viral                 | 7                                                                       | 7          | 6           | 26         | 33                | 0                                                              | 0          |
|          | Gastrointestinal bacterial infection  | 0                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Gastrointestinal bacterial overgrowth | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Gastrointestinal infection            | 4                                                                       | 5          | 2           | 9          | 14                | 0                                                              | 0          |
|          | Gastrointestinal viral infection      | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|          | Genital abscess                       | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Genital herpes                        | 16                                                                      | 18         | 32          | 58         | 76                | 0                                                              | 0          |
|          | Genital herpes simplex                | 1                                                                       | 1          | 2           | 3          | 4                 | 0                                                              | 0          |
|          | Genital herpes zoster                 | 2                                                                       | 2          | 2           | 2          | 4                 | 0                                                              | 0          |
|          | Genital infection bacterial           | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Genital infection female              | 0                                                                       | 0          | 2           | 2          | 2                 | 0                                                              | 0          |
|          | Genital infection fungal              | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Genitourinary tract infection         | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Giardiasis                            | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Gingival abscess                      | 1                                                                       | 1          | 0           | 3          | 4                 | 0                                                              | 0          |
|          | Gingivitis                            | 6                                                                       | 6          | 26          | 48         | 54                | 0                                                              | 0          |
|          | Gonorrhoea                            | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Groin abscess                         | 2                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Groin infection                       | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | H1N1 influenza                        | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|          | HCoV-OC43 infection                   | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Haematoma infection                   | 1                                                                       | 2          | 0           | 1          | 3                 | 0                                                              | 0          |
|          | Haemophilus infection                 | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |

|          |                                            | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|--------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                            | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                         | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Haemorrhagic pneumonia                     | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Hand-foot-and-mouth disease                | 3                                                                       | 3          | 4           | 5          | 8                 | 0                                                              | 0          |
|          | Helicobacter gastritis                     | 0                                                                       | 1          | 2           | 2          | 3                 | 0                                                              | 0          |
|          | Helicobacter infection                     | 4                                                                       | 9          | 1           | 2          | 11                | 0                                                              | 0          |
|          | Helminthic infection                       | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Hepatic infection                          | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Hepatitis B                                | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Hepatitis B reactivation                   | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Hepatitis C                                | 1                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Hepatitis E                                | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Hepatitis infectious mononucleosis         | 1                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Hepatitis viral                            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Herpangina                                 | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Herpes dermatitis                          | 1                                                                       | 1          | 3           | 6          | 7                 | 0                                                              | 0          |
|          | Herpes oesophagitis                        | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Herpes ophthalmic                          | 18                                                                      | 34         | 1           | 2          | 36                | 0                                                              | 0          |
|          | Herpes simplex                             | 13                                                                      | 16         | 46          | 103        | 119               | 0                                                              | 0          |
|          | Herpes simplex encephalitis                | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Herpes simplex meningitis                  | 2                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Herpes simplex oesophagitis                | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Herpes simplex reactivation                | 2                                                                       | 3          | 10          | 19         | 22                | 0                                                              | 0          |
|          | Herpes virus infection                     | 7                                                                       | 16         | 40          | 90         | 106               | 0                                                              | 0          |
|          | Herpes zoster                              | 330                                                                     | 502        | 1153        | 2597       | 3099              | 0                                                              | 0          |
|          | Herpes zoster cutaneous disseminated       | 4                                                                       | 7          | 0           | 0          | 7                 | 0                                                              | 0          |
|          | Herpes zoster disseminated                 | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Herpes zoster infection neurological       | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Herpes zoster meningitis                   | 4                                                                       | 7          | 0           | 0          | 7                 | 0                                                              | 0          |
|          | Herpes zoster meningoencephalitis          | 3                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Herpes zoster meningoradiculitis           | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Herpes zoster oticus                       | 20                                                                      | 32         | 1           | 2          | 34                | 0                                                              | 0          |
|          | Herpes zoster reactivation                 | 7                                                                       | 8          | 16          | 22         | 30                | 0                                                              | 0          |
|          | Herpetic radiculopathy                     | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Histoplasmosis                             | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Hordeolum                                  | 3                                                                       | 6          | 15          | 59         | 65                | 0                                                              | 0          |
|          | Human anaplasmosis                         | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Human ehrlichiosis                         | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Human herpesvirus 6 infection              | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Human herpesvirus 6 infection reactivation | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Hypopyon                                   | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Impetigo                                   | 4                                                                       | 5          | 11          | 14         | 19                | 0                                                              | 0          |
|          | Implant site pustules                      | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Infected bite                              | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Infected bunion                            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Infected cyst                              | 0                                                                       | 2          | 1           | 1          | 3                 | 0                                                              | 0          |
|          | Infected dermal cyst                       | 0                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Infected fistula                           | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Infected skin ulcer                        | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Infection                                  | 127                                                                     | 189        | 119         | 257        | 446               | 0                                                              | 0          |
|          | Infection in an immunocompromised host     | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |

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|----------|---------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                             | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                          | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Infection parasitic                         | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Infection reactivation                      | 0                                                                       | 1          | 1           | 2          | 3                 | 0                                                              | 0          |
|          | Infection susceptibility increased          | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Infection transmission via personal contact | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Infection via vaccinee                      | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Infectious disease carrier                  | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Infectious mononucleosis                    | 5                                                                       | 7          | 9           | 26         | 33                | 0                                                              | 0          |
|          | Infectious pleural effusion                 | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Infective corneal ulcer                     | 0                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Infective glossitis                         | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Infective thrombosis                        | 1                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Influenza                                   | 490                                                                     | 555        | 2337        | 2808       | 3363              | 0                                                              | 0          |
|          | Injection site abscess                      | 1                                                                       | 1          | 5           | 40         | 41                | 0                                                              | 0          |
|          | Injection site cellulitis                   | 8                                                                       | 25         | 3           | 225        | 250               | 0                                                              | 0          |
|          | Injection site infection                    | 4                                                                       | 4          | 14          | 74         | 78                | 0                                                              | 0          |
|          | Injection site pustule                      | 0                                                                       | 1          | 5           | 26         | 27                | 0                                                              | 0          |
|          | Intestinal sepsis                           | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Joint abscess                               | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Keratitis viral                             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Kidney infection                            | 20                                                                      | 51         | 4           | 5          | 56                | 0                                                              | 0          |
|          | Klebsiella bacteraemia                      | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Klebsiella infection                        | 5                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Labyrinthitis                               | 12                                                                      | 19         | 16          | 26         | 45                | 0                                                              | 0          |
|          | Large intestine infection                   | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Laryngitis                                  | 10                                                                      | 11         | 15          | 44         | 55                | 0                                                              | 0          |
|          | Latent tuberculosis                         | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Lice infestation                            | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Lip infection                               | 0                                                                       | 0          | 2           | 3          | 3                 | 0                                                              | 0          |
|          | Listeriosis                                 | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Liver abscess                               | 1                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Localised infection                         | 25                                                                      | 33         | 17          | 51         | 84                | 0                                                              | 0          |
|          | Lower respiratory tract infection           | 58                                                                      | 87         | 10          | 14         | 101               | 0                                                              | 0          |
|          | Lung abscess                                | 4                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Lyme disease                                | 14                                                                      | 37         | 3           | 5          | 42                | 0                                                              | 0          |
|          | Lymph gland infection                       | 2                                                                       | 2          | 2           | 3          | 5                 | 0                                                              | 0          |
|          | Lymph node abscess                          | 2                                                                       | 4          | 1           | 1          | 5                 | 0                                                              | 0          |
|          | Lymph node tuberculosis                     | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Lymphangitis                                | 18                                                                      | 42         | 7           | 8          | 50                | 0                                                              | 0          |
|          | Mastitis                                    | 33                                                                      | 47         | 6           | 8          | 55                | 0                                                              | 0          |
|          | Mastoiditis                                 | 0                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Measles                                     | 1                                                                       | 2          | 2           | 2          | 4                 | 0                                                              | 0          |
|          | Mediastinitis                               | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Medical device site joint infection         | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Meningitis                                  | 27                                                                      | 43         | 0           | 0          | 43                | 0                                                              | 0          |
|          | Meningitis aseptic                          | 28                                                                      | 44         | 0           | 0          | 44                | 0                                                              | 0          |
|          | Meningitis bacterial                        | 2                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Meningitis coxsackie viral                  | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Meningitis herpes                           | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Meningitis viral                            | 10                                                                      | 19         | 0           | 0          | 19                | 0                                                              | 0          |



|          |                                          | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                          | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                       | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Meningoencephalitis bacterial            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Meningoencephalitis herpetic             | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Meningoencephalitis viral                | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Molluscum contagiosum                    | 0                                                                       | 1          | 0           | 3          | 4                 | 0                                                              | 0          |
|          | Mucormycosis                             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Mucosal infection                        | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Mumps                                    | 2                                                                       | 2          | 2           | 4          | 6                 | 0                                                              | 0          |
|          | Muscle abscess                           | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Mycobacterium avium complex infection    | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Myelitis                                 | 32                                                                      | 45         | 0           | 0          | 45                | 0                                                              | 0          |
|          | Myocarditis infectious                   | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Myringitis                               | 2                                                                       | 2          | 2           | 2          | 4                 | 0                                                              | 0          |
|          | Nail infection                           | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Nasal abscess                            | 0                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Nasal herpes                             | 2                                                                       | 2          | 13          | 17         | 19                | 0                                                              | 0          |
|          | Nasal vestibulitis                       | 0                                                                       | 0          | 4           | 5          | 5                 | 0                                                              | 0          |
|          | Nasopharyngitis                          | 251                                                                     | 288        | 958         | 2147       | 2435              | 0                                                              | 0          |
|          | Necrotising fasciitis                    | 2                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Necrotising ulcerative gingivostomatitis | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Neuroborreliosis                         | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Neurological infection                   | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Neutropenic sepsis                       | 0                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Nipple infection                         | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Norovirus infection                      | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Nosocomial infection                     | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Oesophageal candidiasis                  | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Omphalitis                               | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Onychomycosis                            | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Oophoritis                               | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Ophthalmic herpes simplex                | 4                                                                       | 7          | 0           | 1          | 8                 | 0                                                              | 0          |
|          | Ophthalmic herpes zoster                 | 54                                                                      | 89         | 5           | 5          | 94                | 0                                                              | 0          |
|          | Oral candidiasis                         | 8                                                                       | 8          | 9           | 33         | 41                | 0                                                              | 0          |
|          | Oral fungal infection                    | 0                                                                       | 2          | 1           | 6          | 8                 | 0                                                              | 0          |
|          | Oral herpes                              | 68                                                                      | 86         | 307         | 697        | 783               | 0                                                              | 0          |
|          | Oral infection                           | 2                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Oral pustule                             | 0                                                                       | 1          | 1           | 8          | 9                 | 0                                                              | 0          |
|          | Orbital infection                        | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Orchitis                                 | 4                                                                       | 5          | 3           | 5          | 10                | 0                                                              | 0          |
|          | Oropharyngeal candidiasis                | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Osteomyelitis                            | 9                                                                       | 16         | 0           | 1          | 17                | 0                                                              | 0          |
|          | Osteomyelitis acute                      | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Otitis externa                           | 1                                                                       | 2          | 9           | 13         | 15                | 0                                                              | 0          |
|          | Otitis media                             | 1                                                                       | 3          | 7           | 17         | 20                | 0                                                              | 0          |
|          | Otitis media acute                       | 2                                                                       | 2          | 1           | 4          | 6                 | 0                                                              | 0          |
|          | Otitis media chronic                     | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Otosalpingitis                           | 0                                                                       | 0          | 2           | 3          | 3                 | 0                                                              | 0          |
|          | Overgrowth bacterial                     | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Overgrowth fungal                        | 2                                                                       | 2          | 0           | 1          | 3                 | 0                                                              | 0          |
|          | Pancreas infection                       | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |

|          |                                  | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|----------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                  | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                               | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Pancreatitis viral               | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Papilloma viral infection        | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|          | Papular pruritic eruption of HIV | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Parainfluenzae virus infection   | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Parasitic gastroenteritis        | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Paronychia                       | 0                                                                       | 0          | 3           | 5          | 5                 | 0                                                              | 0          |
|          | Parotitis                        | 1                                                                       | 3          | 3           | 11         | 14                | 0                                                              | 0          |
|          | Parvovirus infection             | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|          | Pathogen resistance              | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Pelvic abscess                   | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Pelvic inflammatory disease      | 5                                                                       | 8          | 0           | 0          | 8                 | 0                                                              | 0          |
|          | Peptostreptococcus infection     | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Perichondritis                   | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Pericoronitis                    | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Perineal abscess                 | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Perinephritis                    | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Periodontitis                    | 1                                                                       | 1          | 2           | 2          | 3                 | 0                                                              | 0          |
|          | Periorbital cellulitis           | 1                                                                       | 3          | 0           | 1          | 4                 | 0                                                              | 0          |
|          | Perirectal abscess               | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Peritonitis                      | 4                                                                       | 9          | 0           | 1          | 10                | 0                                                              | 0          |
|          | Peritonitis bacterial            | 0                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Peritonsillar abscess            | 3                                                                       | 8          | 0           | 1          | 9                 | 0                                                              | 0          |
|          | Peritonsillitis                  | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Pertussis                        | 1                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Pharyngeal abscess               | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Pharyngeal pustule               | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|          | Pharyngitis                      | 11                                                                      | 14         | 18          | 40         | 54                | 0                                                              | 0          |
|          | Pharyngitis bacterial            | 0                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Pharyngitis streptococcal        | 3                                                                       | 4          | 3           | 24         | 28                | 0                                                              | 0          |
|          | Pharyngotonsillitis              | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Pilonidal cyst                   | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Plague                           | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Pleural infection                | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Pleurisy viral                   | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Pneumococcal sepsis              | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Pneumocystis jirovecii pneumonia | 3                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Pneumonia                        | 650                                                                     | 1234       | 10          | 21         | 1255              | 0                                                              | 0          |
|          | Pneumonia aspiration             | 28                                                                      | 59         | 0           | 1          | 60                | 0                                                              | 0          |
|          | Pneumonia bacterial              | 37                                                                      | 60         | 2           | 3          | 63                | 0                                                              | 0          |
|          | Pneumonia escherichia            | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Pneumonia fungal                 | 2                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Pneumonia klebsiella             | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Pneumonia legionella             | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Pneumonia mycoplasmal            | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Pneumonia necrotising            | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Pneumonia pneumococcal           | 2                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Pneumonia pseudomonal            | 0                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Pneumonia staphylococcal         | 5                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Pneumonia streptococcal          | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |

|          |                                       | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|---------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                       | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                    | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Pneumonia viral                       | 24                                                                      | 36         | 0           | 2          | 38                | 0                                                              | 0          |
|          | Poliomyelitis                         | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Post procedural infection             | 2                                                                       | 2          | 0           | 1          | 3                 | 0                                                              | 0          |
|          | Post procedural pneumonia             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Post viral fatigue syndrome           | 8                                                                       | 9          | 7           | 14         | 23                | 0                                                              | 0          |
|          | Post-acute COVID-19 syndrome          | 17                                                                      | 20         | 16          | 146        | 166               | 0                                                              | 0          |
|          | Postoperative abscess                 | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Postoperative wound infection         | 4                                                                       | 7          | 0           | 1          | 8                 | 0                                                              | 0          |
|          | Proctitis herpes                      | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Prostate infection                    | 0                                                                       | 3          | 1           | 1          | 4                 | 0                                                              | 0          |
|          | Proteus infection                     | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Pseudomembranous colitis              | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Pseudomonal bacteraemia               | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Pseudomonas infection                 | 5                                                                       | 6          | 0           | 0          | 6                 | 0                                                              | 0          |
|          | Pulmonary tuberculosis                | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Pulpitis dental                       | 1                                                                       | 2          | 8           | 14         | 16                | 0                                                              | 0          |
|          | Purulence                             | 1                                                                       | 2          | 3           | 3          | 5                 | 0                                                              | 0          |
|          | Purulent discharge                    | 3                                                                       | 3          | 0           | 6          | 9                 | 0                                                              | 0          |
|          | Purulent pericarditis                 | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Pustule                               | 6                                                                       | 10         | 36          | 77         | 87                | 0                                                              | 0          |
|          | Pyelitis                              | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Pyelonephritis                        | 16                                                                      | 24         | 0           | 1          | 25                | 0                                                              | 0          |
|          | Pyelonephritis acute                  | 6                                                                       | 7          | 0           | 0          | 7                 | 0                                                              | 0          |
|          | Pyoderma                              | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Pyuria                                | 5                                                                       | 7          | 2           | 4          | 11                | 0                                                              | 0          |
|          | Q fever                               | 4                                                                       | 10         | 1           | 1          | 11                | 0                                                              | 0          |
|          | Rabies                                | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Rash pustular                         | 6                                                                       | 10         | 33          | 71         | 81                | 0                                                              | 0          |
|          | Recurrent subareolar breast abscess   | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Relapsing fever                       | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Renal abscess                         | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Respiratory moniliasis                | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Respiratory syncytial virus infection | 7                                                                       | 7          | 3           | 4          | 11                | 0                                                              | 0          |
|          | Respiratory tract infection           | 12                                                                      | 22         | 3           | 6          | 28                | 0                                                              | 0          |
|          | Respiratory tract infection viral     | 3                                                                       | 3          | 0           | 1          | 4                 | 0                                                              | 0          |
|          | Retinitis viral                       | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Rhinitis                              | 19                                                                      | 22         | 66          | 106        | 128               | 0                                                              | 0          |
|          | Rhinovirus infection                  | 1                                                                       | 2          | 1           | 2          | 4                 | 0                                                              | 0          |
|          | Rickettsiosis                         | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Rocky mountain spotted fever          | 2                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Root canal infection                  | 0                                                                       | 0          | 1           | 4          | 4                 | 0                                                              | 0          |
|          | Roseola                               | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Rotavirus infection                   | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Rubella                               | 2                                                                       | 2          | 0           | 2          | 4                 | 0                                                              | 0          |
|          | SARS-CoV-2 carrier                    | 0                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | SARS-CoV-2 sepsis                     | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Salmonellosis                         | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Salpingitis                           | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Salpingo-oophoritis                   | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |

|          |                                   | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|-----------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                   | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Scarlet fever                     | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|          | Scedosporium infection            | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Schistosomiasis cutaneous         | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Scrotal cellulitis                | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Sebaceous gland infection         | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Secondary transmission            | 0                                                                       | 1          | 1           | 2          | 3                 | 0                                                              | 0          |
|          | Sepsis                            | 229                                                                     | 409        | 3           | 6          | 415               | 0                                                              | 0          |
|          | Septic embolus                    | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Septic encephalopathy             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Septic shock                      | 75                                                                      | 121        | 0           | 0          | 121               | 0                                                              | 0          |
|          | Serratia bacteraemia              | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Serratia infection                | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Severe acute respiratory syndrome | 3                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Sexually transmitted disease      | 0                                                                       | 0          | 1           | 3          | 3                 | 0                                                              | 0          |
|          | Sialoadenitis                     | 4                                                                       | 11         | 1           | 1          | 12                | 0                                                              | 0          |
|          | Sinobronchitis                    | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Sinusitis                         | 51                                                                      | 64         | 164         | 453        | 517               | 0                                                              | 0          |
|          | Sinusitis bacterial               | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Skin bacterial infection          | 2                                                                       | 4          | 1           | 8          | 12                | 0                                                              | 0          |
|          | Skin candida                      | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Skin infection                    | 9                                                                       | 13         | 24          | 73         | 86                | 0                                                              | 0          |
|          | Smallpox                          | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Soft tissue infection             | 1                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Spinal cord infection             | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Spontaneous bacterial peritonitis | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Sputum purulent                   | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Staphylococcal bacteraemia        | 7                                                                       | 11         | 0           | 0          | 11                | 0                                                              | 0          |
|          | Staphylococcal infection          | 31                                                                      | 55         | 5           | 8          | 63                | 0                                                              | 0          |
|          | Staphylococcal pharyngitis        | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Staphylococcal sepsis             | 3                                                                       | 10         | 0           | 0          | 10                | 0                                                              | 0          |
|          | Staphylococcal skin infection     | 2                                                                       | 2          | 1           | 2          | 4                 | 0                                                              | 0          |
|          | Streptococcal bacteraemia         | 4                                                                       | 6          | 0           | 0          | 6                 | 0                                                              | 0          |
|          | Streptococcal infection           | 6                                                                       | 8          | 1           | 5          | 13                | 0                                                              | 0          |
|          | Subcutaneous abscess              | 4                                                                       | 5          | 4           | 14         | 19                | 0                                                              | 0          |
|          | Superinfection                    | 18                                                                      | 20         | 0           | 0          | 20                | 0                                                              | 0          |
|          | Superinfection bacterial          | 1                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Suspected COVID-19                | 17                                                                      | 23         | 90          | 187        | 210               | 0                                                              | 0          |
|          | Sweat gland infection             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Sweating fever                    | 41                                                                      | 49         | 7           | 7          | 56                | 0                                                              | 0          |
|          | Syphilis                          | 1                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Systemic candida                  | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Systemic infection                | 3                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Tetanus                           | 0                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Tinea cruris                      | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Tinea infection                   | 0                                                                       | 0          | 1           | 3          | 3                 | 0                                                              | 0          |
|          | Tinea pedis                       | 0                                                                       | 0          | 3           | 3          | 3                 | 0                                                              | 0          |
|          | Tinea versicolour                 | 0                                                                       | 0          | 2           | 3          | 3                 | 0                                                              | 0          |
|          | Tongue abscess                    | 0                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Tonsillitis                       | 17                                                                      | 22         | 30          | 47         | 69                | 0                                                              | 0          |

|          |                                             | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|---------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                             | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                          | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Tonsillitis bacterial                       | 1                                                                       | 2          | 1           | 1          | 3                 | 0                                                              | 0          |
|          | Tonsillitis streptococcal                   | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Tooth abscess                               | 2                                                                       | 3          | 7           | 24         | 27                | 0                                                              | 0          |
|          | Tooth infection                             | 5                                                                       | 5          | 9           | 37         | 42                | 0                                                              | 0          |
|          | Toxic shock syndrome                        | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Toxocariasis                                | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Toxoplasmosis                               | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Tracheitis                                  | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Tracheobronchitis                           | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Trachoma                                    | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Trichomoniasis                              | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|          | Tuberculosis                                | 2                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Tubo-ovarian abscess                        | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Tularaemia                                  | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Upper respiratory tract infection           | 19                                                                      | 22         | 29          | 57         | 79                | 0                                                              | 0          |
|          | Upper respiratory tract infection bacterial | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Urethritis                                  | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Urinary tract infection                     | 179                                                                     | 355        | 101         | 386        | 741               | 0                                                              | 0          |
|          | Urinary tract infection bacterial           | 0                                                                       | 1          | 1           | 2          | 3                 | 0                                                              | 0          |
|          | Urinary tract infection enterococcal        | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Urinary tract infection staphylococcal      | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Urosepsis                                   | 5                                                                       | 13         | 0           | 0          | 13                | 0                                                              | 0          |
|          | Uterine infection                           | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Vaccination site abscess                    | 2                                                                       | 2          | 6           | 17         | 19                | 0                                                              | 0          |
|          | Vaccination site cellulitis                 | 9                                                                       | 31         | 11          | 120        | 151               | 0                                                              | 0          |
|          | Vaccination site infection                  | 5                                                                       | 10         | 49          | 101        | 111               | 0                                                              | 0          |
|          | Vaccination site joint infection            | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Vaccination site pustule                    | 0                                                                       | 0          | 15          | 23         | 23                | 0                                                              | 0          |
|          | Vaccine breakthrough infection              | 457                                                                     | 471        | 100         | 102        | 573               | 0                                                              | 0          |
|          | Vaccine virus shedding                      | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Vaginal infection                           | 4                                                                       | 4          | 7           | 15         | 19                | 0                                                              | 0          |
|          | Varicella                                   | 8                                                                       | 9          | 13          | 22         | 31                | 0                                                              | 0          |
|          | Varicella post vaccine                      | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|          | Varicella zoster virus infection            | 5                                                                       | 5          | 5           | 9          | 14                | 0                                                              | 0          |
|          | Vascular device infection                   | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Vertical infection transmission             | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Vestibular neuronitis                       | 57                                                                      | 69         | 17          | 35         | 104               | 0                                                              | 0          |
|          | Vestibulitis                                | 1                                                                       | 1          | 1           | 2          | 3                 | 0                                                              | 0          |
|          | Viraemia                                    | 2                                                                       | 3          | 0           | 1          | 4                 | 0                                                              | 0          |
|          | Viral cardiomyopathy                        | 1                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Viral infection                             | 25                                                                      | 40         | 20          | 55         | 95                | 0                                                              | 0          |
|          | Viral labyrinthitis                         | 2                                                                       | 3          | 1           | 2          | 5                 | 0                                                              | 0          |
|          | Viral myocarditis                           | 3                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Viral myositis                              | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Viral parotitis                             | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Viral pericarditis                          | 0                                                                       | 6          | 0           | 0          | 6                 | 0                                                              | 0          |
|          | Viral pharyngitis                           | 2                                                                       | 3          | 1           | 2          | 5                 | 0                                                              | 0          |
|          | Viral rash                                  | 4                                                                       | 6          | 3           | 12         | 18                | 0                                                              | 0          |
|          | Viral sinusitis                             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |

|                                                |                                         | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|------------------------------------------------|-----------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|                                                |                                         | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM                                       | PT                                      | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|                                                | Viral skin infection                    | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                                | Viral tonsillitis                       | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|                                                | Viral upper respiratory tract infection | 2                                                                       | 2          | 2           | 4          | 6                 | 0                                                              | 0          |
|                                                | Viral uveitis                           | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                                                | Vitritis infective                      | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                                | Vulval abscess                          | 0                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|                                                | Vulval cellulitis                       | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                                | Vulvitis                                | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                                | Vulvovaginal candidiasis                | 3                                                                       | 3          | 7           | 13         | 16                | 0                                                              | 0          |
|                                                | Vulvovaginal mycotic infection          | 2                                                                       | 2          | 14          | 23         | 25                | 0                                                              | 0          |
|                                                | Vulvovaginitis                          | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                                | Wound abscess                           | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                                                | Wound infection                         | 4                                                                       | 6          | 1           | 2          | 8                 | 0                                                              | 0          |
|                                                | Wound infection bacterial               | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                                | Zika virus infection                    | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
| Injury, poisoning and procedural complications | *** SOC TOTAL ***                       | 2714                                                                    | 4252       | 18916       | 44570      | 48822             | 0                                                              | 0          |
|                                                | Abdomen crushing                        | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                                | Accident                                | 2                                                                       | 5          | 2           | 12         | 17                | 0                                                              | 0          |
|                                                | Accident at home                        | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|                                                | Accident at work                        | 2                                                                       | 2          | 1           | 3          | 5                 | 0                                                              | 0          |
|                                                | Accidental exposure to product          | 1                                                                       | 2          | 6           | 34         | 36                | 0                                                              | 0          |
|                                                | Accidental overdose                     | 3                                                                       | 7          | 383         | 498        | 505               | 0                                                              | 0          |
|                                                | Accidental underdose                    | 0                                                                       | 0          | 205         | 355        | 355               | 0                                                              | 0          |
|                                                | Acetabulum fracture                     | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                                | Administration related reaction         | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|                                                | Adverse event following immunisation    | 0                                                                       | 1          | 7           | 30         | 31                | 0                                                              | 0          |
|                                                | Airway burns                            | 0                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|                                                | Airway complication of anaesthesia      | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                                | Alcohol poisoning                       | 2                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|                                                | Anaesthetic complication                | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                                                | Animal bite                             | 1                                                                       | 1          | 3           | 11         | 12                | 0                                                              | 0          |
|                                                | Animal scratch                          | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|                                                | Ankle fracture                          | 6                                                                       | 14         | 1           | 8          | 22                | 0                                                              | 0          |
|                                                | Arterial injury                         | 2                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|                                                | Arteriovenous fistula site haemorrhage  | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                                | Arteriovenous fistula thrombosis        | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                                | Arthropod bite                          | 2                                                                       | 5          | 12          | 37         | 42                | 0                                                              | 0          |
|                                                | Arthropod sting                         | 0                                                                       | 1          | 8           | 21         | 22                | 0                                                              | 0          |
|                                                | Avulsion fracture                       | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|                                                | Axillary nerve injury                   | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                                | Axillary web syndrome                   | 0                                                                       | 1          | 0           | 2          | 3                 | 0                                                              | 0          |
|                                                | Back injury                             | 5                                                                       | 8          | 2           | 28         | 36                | 0                                                              | 0          |
|                                                | Barotitis media                         | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|                                                | Barotrauma                              | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|                                                | Bite                                    | 1                                                                       | 1          | 0           | 10         | 11                | 0                                                              | 0          |
|                                                | Bladder injury                          | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                                                | Bone contusion                          | 2                                                                       | 2          | 0           | 3          | 5                 | 0                                                              | 0          |
|                                                | Bone fissure                            | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|                                                | Bone fragmentation                      | 0                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |

|          |                                            | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|--------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                            | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                         | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Booster dose missed                        | 0                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Brachial plexus injury                     | 2                                                                       | 3          | 0           | 1          | 4                 | 0                                                              | 0          |
|          | Brain contusion                            | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Brain herniation                           | 9                                                                       | 17         | 0           | 0          | 17                | 0                                                              | 0          |
|          | Burn oesophageal                           | 1                                                                       | 1          | 2           | 4          | 5                 | 0                                                              | 0          |
|          | Burn oral cavity                           | 1                                                                       | 4          | 0           | 2          | 6                 | 0                                                              | 0          |
|          | Burns first degree                         | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Burns second degree                        | 3                                                                       | 4          | 2           | 6          | 10                | 0                                                              | 0          |
|          | Burns third degree                         | 2                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Bursa injury                               | 0                                                                       | 0          | 1           | 3          | 3                 | 0                                                              | 0          |
|          | Buttock injury                             | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Carbon monoxide poisoning                  | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Cardiac procedure complication             | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Cardiac septal defect residual shunt       | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Cardiac vein dissection                    | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Cartilage injury                           | 1                                                                       | 3          | 2           | 3          | 6                 | 0                                                              | 0          |
|          | Central nervous system injury              | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Cerebral ventricle collapse                | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Cervical vertebral fracture                | 3                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Chemical burn                              | 0                                                                       | 0          | 0           | 4          | 4                 | 0                                                              | 0          |
|          | Chemical poisoning                         | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Chest crushing                             | 2                                                                       | 5          | 2           | 2          | 7                 | 0                                                              | 0          |
|          | Chest injury                               | 6                                                                       | 16         | 0           | 0          | 16                | 0                                                              | 0          |
|          | Child maltreatment syndrome                | 1                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Chillblains                                | 6                                                                       | 9          | 22          | 51         | 60                | 0                                                              | 0          |
|          | Circumstance or information capable of lea | 0                                                                       | 0          | 0           | 9          | 9                 | 0                                                              | 0          |
|          | Clavicle fracture                          | 4                                                                       | 9          | 5           | 6          | 15                | 0                                                              | 0          |
|          | Cold burn                                  | 1                                                                       | 1          | 1           | 2          | 3                 | 0                                                              | 0          |
|          | Colon injury                               | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|          | Complicated fracture                       | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Complications of transplant surgery        | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Complications of transplanted kidney       | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Complications of transplanted lung         | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Compression fracture                       | 1                                                                       | 4          | 0           | 2          | 6                 | 0                                                              | 0          |
|          | Concussion                                 | 21                                                                      | 40         | 18          | 60         | 100               | 0                                                              | 0          |
|          | Conjunctival scar                          | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|          | Contraindicated product administered       | 0                                                                       | 0          | 0           | 3          | 3                 | 0                                                              | 0          |
|          | Contraindicated product prescribed         | 1                                                                       | 2          | 0           | 1          | 3                 | 0                                                              | 0          |
|          | Contusion                                  | 250                                                                     | 359        | 521         | 1594       | 1953              | 0                                                              | 0          |
|          | Corneal abrasion                           | 1                                                                       | 2          | 1           | 5          | 7                 | 0                                                              | 0          |
|          | Corneal laceration                         | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Coronary artery reocclusion                | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Coronary vascular graft occlusion          | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Counterfeit product administered           | 0                                                                       | 0          | 1           | 5          | 5                 | 0                                                              | 0          |
|          | Cranial nerve injury                       | 0                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Craniocerebral injury                      | 7                                                                       | 16         | 1           | 2          | 18                | 0                                                              | 0          |
|          | Dental leakage                             | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Dermal filler overcorrection               | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Device difficult to use                    | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |

|          |                                           | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|-------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                           | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                        | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Device dispensing error                   | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Device use confusion                      | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|          | Device use error                          | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|          | Device use issue                          | 0                                                                       | 0          | 0           | 5          | 5                 | 0                                                              | 0          |
|          | Dialysis related complication             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Dislocation of vertebra                   | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Documented hypersensitivity to administer | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Dose calculation error                    | 0                                                                       | 0          | 0           | 5          | 5                 | 0                                                              | 0          |
|          | Drain site complication                   | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Drug administered in wrong device         | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Drug dispensed to wrong patient           | 0                                                                       | 0          | 0           | 4          | 4                 | 0                                                              | 0          |
|          | Drug dose omission by device              | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Duplicate therapy error                   | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Ear injury                                | 0                                                                       | 0          | 1           | 3          | 3                 | 0                                                              | 0          |
|          | Electric shock                            | 5                                                                       | 5          | 1           | 6          | 11                | 0                                                              | 0          |
|          | Endotracheal intubation complication      | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Epicondylitis                             | 5                                                                       | 6          | 14          | 21         | 27                | 0                                                              | 0          |
|          | Eschar                                    | 1                                                                       | 1          | 1           | 3          | 4                 | 0                                                              | 0          |
|          | Expired device used                       | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Expired product administered              | 2                                                                       | 3          | 5420        | 6224       | 6227              | 0                                                              | 0          |
|          | Exposure during pregnancy                 | 80                                                                      | 138        | 156         | 1277       | 1415              | 0                                                              | 0          |
|          | Exposure to SARS-CoV-2                    | 87                                                                      | 101        | 161         | 258        | 359               | 0                                                              | 0          |
|          | Exposure to communicable disease          | 2                                                                       | 3          | 0           | 1          | 4                 | 0                                                              | 0          |
|          | Exposure to contaminated air              | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Exposure to contaminated device           | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Exposure to extreme temperature           | 1                                                                       | 3          | 1           | 3          | 6                 | 0                                                              | 0          |
|          | Exposure to noise                         | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Exposure to tobacco                       | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Exposure to toxic agent                   | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Exposure to vaccinated person             | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Exposure via body fluid                   | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Exposure via breast milk                  | 34                                                                      | 46         | 232         | 495        | 541               | 0                                                              | 0          |
|          | Exposure via contaminated device          | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Exposure via direct contact               | 2                                                                       | 2          | 1           | 1          | 3                 | 0                                                              | 0          |
|          | Exposure via eye contact                  | 0                                                                       | 0          | 0           | 4          | 4                 | 0                                                              | 0          |
|          | Exposure via skin contact                 | 0                                                                       | 1          | 1           | 98         | 99                | 0                                                              | 0          |
|          | Exposure via unknown route                | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Extra dose administered                   | 39                                                                      | 40         | 239         | 572        | 612               | 0                                                              | 0          |
|          | Extradural haematoma                      | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Extraskkeletal ossification               | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Eye contusion                             | 3                                                                       | 6          | 8           | 40         | 46                | 0                                                              | 0          |
|          | Eye injury                                | 6                                                                       | 8          | 1           | 12         | 20                | 0                                                              | 0          |
|          | Eyelid contusion                          | 0                                                                       | 0          | 1           | 3          | 3                 | 0                                                              | 0          |
|          | Eyelid injury                             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Face injury                               | 10                                                                      | 14         | 15          | 77         | 91                | 0                                                              | 0          |
|          | Facial bones fracture                     | 2                                                                       | 18         | 0           | 2          | 20                | 0                                                              | 0          |
|          | Fall                                      | 485                                                                     | 938        | 462         | 1736       | 2674              | 0                                                              | 0          |
|          | Fallopian tube perforation                | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Femoral neck fracture                     | 2                                                                       | 7          | 0           | 0          | 7                 | 0                                                              | 0          |



|          |                                                   | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|---------------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                                   | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                                | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Femoral nerve injury                              | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Femur fracture                                    | 8                                                                       | 15         | 0           | 0          | 15                | 0                                                              | 0          |
|          | Fibula fracture                                   | 1                                                                       | 3          | 0           | 1          | 4                 | 0                                                              | 0          |
|          | Foetal exposure during pregnancy                  | 6                                                                       | 7          | 6           | 13         | 20                | 0                                                              | 0          |
|          | Foot fracture                                     | 6                                                                       | 11         | 1           | 12         | 23                | 0                                                              | 0          |
|          | Forearm fracture                                  | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Foreign body                                      | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Foreign body in eye                               | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|          | Foreign body in gastrointestinal tract            | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Foreign body in skin or subcutaneous tissue       | 0                                                                       | 0          | 2           | 2          | 2                 | 0                                                              | 0          |
|          | Foreign body in throat                            | 0                                                                       | 5          | 0           | 2          | 7                 | 0                                                              | 0          |
|          | Foreign body ingestion                            | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Fracture                                          | 8                                                                       | 14         | 7           | 9          | 23                | 0                                                              | 0          |
|          | Fracture displacement                             | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Fractured coccyx                                  | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Fractured sacrum                                  | 1                                                                       | 1          | 1           | 2          | 3                 | 0                                                              | 0          |
|          | Frostbite                                         | 1                                                                       | 1          | 0           | 2          | 3                 | 0                                                              | 0          |
|          | Gastrointestinal anastomotic leak                 | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Gastrointestinal injury                           | 1                                                                       | 2          | 1           | 2          | 4                 | 0                                                              | 0          |
|          | Gastrointestinal stoma complication               | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Gingival injury                                   | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Graft haemorrhage                                 | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Graft thrombosis                                  | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Gun shot wound                                    | 1                                                                       | 2          | 1           | 1          | 3                 | 0                                                              | 0          |
|          | Hair injury                                       | 0                                                                       | 0          | 2           | 4          | 4                 | 0                                                              | 0          |
|          | Hand fracture                                     | 4                                                                       | 6          | 0           | 4          | 10                | 0                                                              | 0          |
|          | Head injury                                       | 65                                                                      | 149        | 70          | 434        | 583               | 0                                                              | 0          |
|          | Heat exhaustion                                   | 1                                                                       | 1          | 1           | 6          | 7                 | 0                                                              | 0          |
|          | Heat illness                                      | 2                                                                       | 2          | 2           | 6          | 8                 | 0                                                              | 0          |
|          | Heat oedema                                       | 2                                                                       | 2          | 6           | 9          | 11                | 0                                                              | 0          |
|          | Heat stroke                                       | 7                                                                       | 8          | 4           | 5          | 13                | 0                                                              | 0          |
|          | Heavy exposure to ultraviolet light               | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|          | Hip fracture                                      | 13                                                                      | 33         | 1           | 1          | 34                | 0                                                              | 0          |
|          | Humerus fracture                                  | 3                                                                       | 6          | 0           | 0          | 6                 | 0                                                              | 0          |
|          | Hypobarism                                        | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Inadequate aseptic technique in use of product    | 0                                                                       | 0          | 0           | 5          | 5                 | 0                                                              | 0          |
|          | Inappropriate schedule of product administration  | 89                                                                      | 94         | 2469        | 4753       | 4847              | 0                                                              | 0          |
|          | Inappropriate schedule of product discontinuation | 0                                                                       | 0          | 2           | 4          | 4                 | 0                                                              | 0          |
|          | Incarcerated incisional hernia                    | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Incision site complication                        | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Incision site discharge                           | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Incision site erythema                            | 1                                                                       | 2          | 0           | 1          | 3                 | 0                                                              | 0          |
|          | Incision site haemorrhage                         | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Incision site impaired healing                    | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Incision site inflammation                        | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Incision site pain                                | 1                                                                       | 1          | 2           | 3          | 4                 | 0                                                              | 0          |
|          | Incision site rash                                | 1                                                                       | 1          | 0           | 2          | 3                 | 0                                                              | 0          |
|          | Incision site swelling                            | 0                                                                       | 1          | 3           | 6          | 7                 | 0                                                              | 0          |
|          | Incisional hernia                                 | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |

|          |                                                 | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|-------------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                                 | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                              | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Incomplete course of vaccination                | 26                                                                      | 33         | 29          | 159        | 192               | 0                                                              | 0          |
|          | Incorrect disposal of product                   | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Incorrect dosage administered                   | 0                                                                       | 0          | 3           | 6          | 6                 | 0                                                              | 0          |
|          | Incorrect dose administered                     | 6                                                                       | 7          | 139         | 970        | 977               | 0                                                              | 0          |
|          | Incorrect dose administered by device           | 0                                                                       | 0          | 0           | 8          | 8                 | 0                                                              | 0          |
|          | Incorrect dose administered by product          | 0                                                                       | 0          | 2           | 6          | 6                 | 0                                                              | 0          |
|          | Incorrect drug administration rate              | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Incorrect product administration duration       | 0                                                                       | 0          | 27          | 33         | 33                | 0                                                              | 0          |
|          | Incorrect product dosage form administered      | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Incorrect product formulation administered      | 0                                                                       | 0          | 8           | 61         | 61                | 0                                                              | 0          |
|          | Incorrect route of product administration       | 8                                                                       | 18         | 220         | 809        | 827               | 0                                                              | 0          |
|          | Induced abortion failed                         | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Inflammation of wound                           | 2                                                                       | 2          | 1           | 2          | 4                 | 0                                                              | 0          |
|          | Infusion related reaction                       | 1                                                                       | 1          | 3           | 8          | 9                 | 0                                                              | 0          |
|          | Injection related reaction                      | 19                                                                      | 21         | 11          | 16         | 37                | 0                                                              | 0          |
|          | Injury                                          | 26                                                                      | 37         | 26          | 51         | 88                | 0                                                              | 0          |
|          | Injury corneal                                  | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Intentional dose omission                       | 0                                                                       | 0          | 70          | 159        | 159               | 0                                                              | 0          |
|          | Intentional overdose                            | 2                                                                       | 3          | 1           | 1          | 4                 | 0                                                              | 0          |
|          | Intentional product misuse                      | 0                                                                       | 0          | 5           | 8          | 8                 | 0                                                              | 0          |
|          | Intentional product use issue                   | 1                                                                       | 2          | 62          | 213        | 215               | 0                                                              | 0          |
|          | Intentional removal of drug delivery system     | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Intentional underdose                           | 0                                                                       | 0          | 3           | 6          | 6                 | 0                                                              | 0          |
|          | Intercepted product administration error        | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|          | Intercepted product prescribing error           | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Intercepted product storage error               | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Intervertebral disc injury                      | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Jaw fracture                                    | 4                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Joint dislocation                               | 9                                                                       | 13         | 5           | 22         | 35                | 0                                                              | 0          |
|          | Joint injury                                    | 18                                                                      | 25         | 13          | 65         | 90                | 0                                                              | 0          |
|          | Labelled drug-drug interaction issue            | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Labelled drug-food interaction medication error | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Lack of injection site rotation                 | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Ligament rupture                                | 1                                                                       | 2          | 3           | 7          | 9                 | 0                                                              | 0          |
|          | Ligament sprain                                 | 3                                                                       | 5          | 15          | 42         | 47                | 0                                                              | 0          |
|          | Limb crushing injury                            | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Limb injury                                     | 45                                                                      | 62         | 33          | 118        | 180               | 0                                                              | 0          |
|          | Lip injury                                      | 7                                                                       | 10         | 5           | 23         | 33                | 0                                                              | 0          |
|          | Lower limb fracture                             | 4                                                                       | 10         | 1           | 3          | 13                | 0                                                              | 0          |
|          | Lumbar vertebral fracture                       | 2                                                                       | 6          | 0           | 0          | 6                 | 0                                                              | 0          |
|          | Maternal exposure before pregnancy              | 7                                                                       | 8          | 40          | 59         | 67                | 0                                                              | 0          |
|          | Maternal exposure during breast feeding         | 180                                                                     | 215        | 359         | 604        | 819               | 0                                                              | 0          |
|          | Maternal exposure during delivery               | 0                                                                       | 0          | 0           | 3          | 3                 | 0                                                              | 0          |
|          | Maternal exposure during pregnancy              | 231                                                                     | 289        | 547         | 1660       | 1949              | 0                                                              | 0          |
|          | Maternal exposure timing unspecified            | 2                                                                       | 2          | 7           | 25         | 27                | 0                                                              | 0          |
|          | Medication error                                | 9                                                                       | 11         | 19          | 81         | 92                | 0                                                              | 0          |
|          | Meningitis chemical                             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Meniscus cyst                                   | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Meniscus injury                                 | 1                                                                       | 2          | 1           | 4          | 6                 | 0                                                              | 0          |

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|----------|-------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                     | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                  | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Metal poisoning                     | 1                                                                       | 2          | 0           | 1          | 3                 | 0                                                              | 0          |
|          | Mouth injury                        | 3                                                                       | 7          | 7           | 14         | 21                | 0                                                              | 0          |
|          | Multiple fractures                  | 3                                                                       | 6          | 0           | 0          | 6                 | 0                                                              | 0          |
|          | Multiple injuries                   | 1                                                                       | 1          | 0           | 3          | 4                 | 0                                                              | 0          |
|          | Multiple use of single-use product  | 0                                                                       | 0          | 0           | 3          | 3                 | 0                                                              | 0          |
|          | Muscle contusion                    | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Muscle injury                       | 8                                                                       | 11         | 4           | 10         | 21                | 0                                                              | 0          |
|          | Muscle rupture                      | 3                                                                       | 5          | 1           | 1          | 6                 | 0                                                              | 0          |
|          | Muscle strain                       | 12                                                                      | 22         | 19          | 76         | 98                | 0                                                              | 0          |
|          | Musculoskeletal injury              | 2                                                                       | 2          | 1           | 1          | 3                 | 0                                                              | 0          |
|          | Nail injury                         | 0                                                                       | 1          | 1           | 2          | 3                 | 0                                                              | 0          |
|          | Nasal injury                        | 4                                                                       | 5          | 2           | 14         | 19                | 0                                                              | 0          |
|          | Neck crushing                       | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Neck injury                         | 0                                                                       | 3          | 1           | 14         | 17                | 0                                                              | 0          |
|          | Nerve injury                        | 37                                                                      | 59         | 43          | 73         | 132               | 0                                                              | 0          |
|          | Nerve root injury                   | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Nervous system injury               | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Occupational exposure to SARS-CoV-2 | 1                                                                       | 1          | 10          | 12         | 13                | 0                                                              | 0          |
|          | Occupational exposure to product    | 0                                                                       | 0          | 7           | 18         | 18                | 0                                                              | 0          |
|          | Ocular procedural complication      | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Oesophageal injury                  | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Off label use                       | 9                                                                       | 12         | 346         | 554        | 566               | 0                                                              | 0          |
|          | Open globe injury                   | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Optic nerve injury                  | 4                                                                       | 7          | 0           | 0          | 7                 | 0                                                              | 0          |
|          | Oral contusion                      | 2                                                                       | 3          | 2           | 8          | 11                | 0                                                              | 0          |
|          | Oral mucosal scar                   | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Oropharyngeal stenosis              | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Osteochondral fracture              | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Overdose                            | 12                                                                      | 12         | 53          | 90         | 102               | 0                                                              | 0          |
|          | Palate injury                       | 0                                                                       | 0          | 0           | 3          | 3                 | 0                                                              | 0          |
|          | Patella fracture                    | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Paternal exposure before pregnancy  | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Pelvic fracture                     | 4                                                                       | 8          | 0           | 0          | 8                 | 0                                                              | 0          |
|          | Perineal injury                     | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Periorbital haematoma               | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Periorbital haemorrhage             | 0                                                                       | 0          | 1           | 7          | 7                 | 0                                                              | 0          |
|          | Peripancreatic fluid collection     | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Peripheral nerve injury             | 1                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Periprosthetic fracture             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Phrenic nerve injury                | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Pneumocephalus                      | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Pneumoconiosis                      | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Poisoning                           | 2                                                                       | 3          | 1           | 1          | 4                 | 0                                                              | 0          |
|          | Poor quality product administered   | 0                                                                       | 0          | 80          | 1767       | 1767              | 0                                                              | 0          |
|          | Post concussion syndrome            | 2                                                                       | 2          | 1           | 3          | 5                 | 0                                                              | 0          |
|          | Post lumbar puncture syndrome       | 0                                                                       | 0          | 2           | 2          | 2                 | 0                                                              | 0          |
|          | Post procedural complication        | 2                                                                       | 6          | 1           | 6          | 12                | 0                                                              | 0          |
|          | Post procedural discharge           | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Post procedural discomfort          | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |

|          |                                             | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|---------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                             | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                          | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Post procedural erythema                    | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Post procedural fever                       | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Post procedural haemorrhage                 | 3                                                                       | 4          | 0           | 1          | 5                 | 0                                                              | 0          |
|          | Post procedural hypothyroidism              | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Post procedural swelling                    | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Post procedural urine leak                  | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Post vaccination syndrome                   | 2                                                                       | 2          | 0           | 1          | 3                 | 0                                                              | 0          |
|          | Post-traumatic neck syndrome                | 1                                                                       | 1          | 3           | 4          | 5                 | 0                                                              | 0          |
|          | Post-traumatic pain                         | 1                                                                       | 1          | 5           | 9          | 10                | 0                                                              | 0          |
|          | Postoperative ileus                         | 0                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Postoperative thrombosis                    | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Postoperative wound complication            | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Prescribed overdose                         | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Procedural complication                     | 1                                                                       | 1          | 0           | 2          | 3                 | 0                                                              | 0          |
|          | Procedural dizziness                        | 1                                                                       | 2          | 2           | 3          | 5                 | 0                                                              | 0          |
|          | Procedural haemorrhage                      | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Procedural pain                             | 1                                                                       | 2          | 4           | 15         | 17                | 0                                                              | 0          |
|          | Procedural site reaction                    | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Procedural vomiting                         | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Product administered at inappropriate site  | 12                                                                      | 27         | 29          | 275        | 302               | 0                                                              | 0          |
|          | Product administered by wrong person        | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Product administered to patient of inappro  | 3                                                                       | 5          | 507         | 4365       | 4370              | 0                                                              | 0          |
|          | Product administration error                | 3                                                                       | 3          | 173         | 364        | 367               | 0                                                              | 0          |
|          | Product administration interrupted          | 0                                                                       | 0          | 23          | 65         | 65                | 0                                                              | 0          |
|          | Product dispensing error                    | 0                                                                       | 0          | 1           | 4          | 4                 | 0                                                              | 0          |
|          | Product dispensing issue                    | 0                                                                       | 0          | 0           | 11         | 11                | 0                                                              | 0          |
|          | Product dosage form confusion               | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Product dose omission in error              | 0                                                                       | 0          | 2           | 18         | 18                | 0                                                              | 0          |
|          | Product dose omission issue                 | 10                                                                      | 13         | 1398        | 3135       | 3148              | 0                                                              | 0          |
|          | Product label confusion                     | 0                                                                       | 0          | 0           | 44         | 44                | 0                                                              | 0          |
|          | Product monitoring error                    | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|          | Product packaging confusion                 | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Product preparation error                   | 0                                                                       | 0          | 10          | 25         | 25                | 0                                                              | 0          |
|          | Product preparation issue                   | 0                                                                       | 1          | 9           | 48         | 49                | 0                                                              | 0          |
|          | Product prescribing issue                   | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Product selection error                     | 0                                                                       | 0          | 2           | 4          | 4                 | 0                                                              | 0          |
|          | Product storage error                       | 1                                                                       | 2          | 1625        | 2917       | 2919              | 0                                                              | 0          |
|          | Product substitution error                  | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Product use complaint                       | 0                                                                       | 0          | 1           | 3          | 3                 | 0                                                              | 0          |
|          | Product use in unapproved indication        | 0                                                                       | 0          | 2           | 3          | 3                 | 0                                                              | 0          |
|          | Product use issue                           | 4                                                                       | 4          | 5           | 15         | 19                | 0                                                              | 0          |
|          | Pulmonary contusion                         | 2                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Radial head dislocation                     | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Radial nerve injury                         | 3                                                                       | 3          | 0           | 2          | 5                 | 0                                                              | 0          |
|          | Radiation associated pain                   | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Radiation injury                            | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Radius fracture                             | 2                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Reaction to previous exposure to any vaccin | 0                                                                       | 0          | 0           | 28         | 28                | 0                                                              | 0          |
|          | Recalled product administered               | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |

|          |                               | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|-------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                               | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                            | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Rectal injury                 | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Retinal injury                | 0                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Rib fracture                  | 11                                                                      | 25         | 7           | 21         | 46                | 0                                                              | 0          |
|          | Road traffic accident         | 20                                                                      | 39         | 7           | 20         | 59                | 0                                                              | 0          |
|          | Sacroiliac fracture           | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Scapula fracture              | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Scar                          | 9                                                                       | 14         | 31          | 75         | 89                | 0                                                              | 0          |
|          | Sciatic nerve injury          | 0                                                                       | 0          | 2           | 3          | 3                 | 0                                                              | 0          |
|          | Scratch                       | 1                                                                       | 2          | 23          | 83         | 85                | 0                                                              | 0          |
|          | Seroma                        | 1                                                                       | 3          | 0           | 1          | 4                 | 0                                                              | 0          |
|          | Shunt malfunction             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Skeletal injury               | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Skin abrasion                 | 7                                                                       | 10         | 17          | 85         | 95                | 0                                                              | 0          |
|          | Skin injury                   | 2                                                                       | 2          | 6           | 15         | 17                | 0                                                              | 0          |
|          | Skin laceration               | 22                                                                      | 43         | 13          | 62         | 105               | 0                                                              | 0          |
|          | Skin wound                    | 0                                                                       | 2          | 5           | 10         | 12                | 0                                                              | 0          |
|          | Skull fracture                | 4                                                                       | 9          | 0           | 1          | 10                | 0                                                              | 0          |
|          | Soft tissue injury            | 1                                                                       | 1          | 0           | 2          | 3                 | 0                                                              | 0          |
|          | Spinal column injury          | 3                                                                       | 3          | 1           | 1          | 4                 | 0                                                              | 0          |
|          | Spinal compression fracture   | 8                                                                       | 21         | 0           | 0          | 21                | 0                                                              | 0          |
|          | Spinal cord injury            | 3                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Spinal cord injury cervical   | 4                                                                       | 7          | 0           | 0          | 7                 | 0                                                              | 0          |
|          | Spinal cord injury thoracic   | 5                                                                       | 6          | 0           | 0          | 6                 | 0                                                              | 0          |
|          | Spinal fracture               | 6                                                                       | 11         | 0           | 0          | 11                | 0                                                              | 0          |
|          | Splenic injury                | 2                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Splenic rupture               | 0                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Splenosis                     | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Splinter                      | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Stab wound                    | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Sternal fracture              | 0                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Stoma site discomfort         | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Stoma site hypergranulation   | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Stoma site oedema             | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Stoma site pain               | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Stoma site rash               | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Stress fracture               | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Subarachnoid haematoma        | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Subcutaneous haematoma        | 3                                                                       | 6          | 3           | 6          | 12                | 0                                                              | 0          |
|          | Subdural haematoma            | 17                                                                      | 52         | 0           | 0          | 52                | 0                                                              | 0          |
|          | Subdural haemorrhage          | 3                                                                       | 9          | 0           | 0          | 9                 | 0                                                              | 0          |
|          | Sunburn                       | 5                                                                       | 7          | 17          | 66         | 73                | 0                                                              | 0          |
|          | Surgical procedure repeated   | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Suture rupture                | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Synovial rupture              | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|          | Systemic toxicity             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Tendon dislocation            | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Tendon injury                 | 5                                                                       | 5          | 3           | 8          | 13                | 0                                                              | 0          |
|          | Tendon rupture                | 6                                                                       | 11         | 4           | 10         | 21                | 0                                                              | 0          |
|          | Tensor fasciae latae syndrome | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |

|          |                                    | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                    | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                 | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Thermal burn                       | 8                                                                       | 8          | 22          | 48         | 56                | 0                                                              | 0          |
|          | Thermal burns of eye               | 4                                                                       | 9          | 1           | 3          | 12                | 0                                                              | 0          |
|          | Thoracic vertebral fracture        | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Tibia fracture                     | 6                                                                       | 8          | 0           | 1          | 9                 | 0                                                              | 0          |
|          | Tissue injury                      | 0                                                                       | 0          | 1           | 6          | 6                 | 0                                                              | 0          |
|          | Tongue injury                      | 2                                                                       | 4          | 0           | 6          | 10                | 0                                                              | 0          |
|          | Tooth avulsion                     | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Tooth fracture                     | 4                                                                       | 4          | 9           | 28         | 32                | 0                                                              | 0          |
|          | Tooth injury                       | 3                                                                       | 3          | 2           | 17         | 20                | 0                                                              | 0          |
|          | Toxicity to various agents         | 2                                                                       | 5          | 2           | 4          | 9                 | 0                                                              | 0          |
|          | Tracheal deviation                 | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Tracheal haemorrhage               | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Tracheal injury                    | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Tracheal obstruction               | 0                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Transcription medication error     | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|          | Transplant dysfunction             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Traumatic arthropathy              | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Traumatic fracture                 | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Traumatic haematoma                | 3                                                                       | 4          | 1           | 4          | 8                 | 0                                                              | 0          |
|          | Traumatic haemorrhage              | 2                                                                       | 3          | 1           | 2          | 5                 | 0                                                              | 0          |
|          | Traumatic haemothorax              | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Traumatic intracranial haemorrhage | 0                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Traumatic lumbar puncture          | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Traumatic lung injury              | 4                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Traumatic renal injury             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Trunk injury                       | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Ulna fracture                      | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Ulnar nerve injury                 | 1                                                                       | 1          | 1           | 2          | 3                 | 0                                                              | 0          |
|          | Underdose                          | 1                                                                       | 2          | 115         | 1080       | 1082              | 0                                                              | 0          |
|          | Upper limb fracture                | 4                                                                       | 10         | 2           | 5          | 15                | 0                                                              | 0          |
|          | VIIIth nerve injury                | 1                                                                       | 1          | 0           | 2          | 3                 | 0                                                              | 0          |
|          | Vaccination complication           | 245                                                                     | 337        | 1863        | 3817       | 4154              | 0                                                              | 0          |
|          | Vaccination error                  | 1                                                                       | 1          | 67          | 122        | 123               | 0                                                              | 0          |
|          | Vascular access site bruising      | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Vascular access site swelling      | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|          | Vascular access site thrombosis    | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Vascular graft occlusion           | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Vascular graft thrombosis          | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Vascular injury                    | 5                                                                       | 6          | 4           | 8          | 14                | 0                                                              | 0          |
|          | Vascular pseudoaneurysm            | 2                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Vasoplegia syndrome                | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Venous injury                      | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Vulvovaginal injury                | 0                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Weaning failure                    | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Wound                              | 26                                                                      | 30         | 19          | 60         | 90                | 0                                                              | 0          |
|          | Wound complication                 | 7                                                                       | 7          | 4           | 8          | 15                | 0                                                              | 0          |
|          | Wound dehiscence                   | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Wound haematoma                    | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Wound haemorrhage                  | 3                                                                       | 4          | 10          | 20         | 24                | 0                                                              | 0          |

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|----------------|---------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|                |                                             | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM       | PT                                          | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|                | Wound necrosis                              | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                | Wound secretion                             | 2                                                                       | 3          | 2           | 7          | 10                | 0                                                              | 0          |
|                | Wrist fracture                              | 3                                                                       | 3          | 2           | 8          | 11                | 0                                                              | 0          |
|                | Wrong dose                                  | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|                | Wrong drug                                  | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|                | Wrong patient                               | 0                                                                       | 0          | 0           | 3          | 3                 | 0                                                              | 0          |
|                | Wrong patient received product              | 0                                                                       | 0          | 0           | 7          | 7                 | 0                                                              | 0          |
|                | Wrong product administered                  | 3                                                                       | 3          | 19          | 281        | 284               | 0                                                              | 0          |
|                | Wrong route                                 | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|                | Wrong schedule                              | 1                                                                       | 1          | 2           | 5          | 6                 | 0                                                              | 0          |
|                | Wrong technique in device usage process     | 1                                                                       | 1          | 14          | 76         | 77                | 0                                                              | 0          |
|                | Wrong technique in product usage process    | 5                                                                       | 5          | 28          | 132        | 137               | 0                                                              | 0          |
| Investigations | *** SOC TOTAL ***                           | 11939                                                                   | 13363      | 7398        | 15734      | 29097             | 0                                                              | 0          |
|                | AST/ALT ratio                               | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                | Abdominal X-ray                             | 4                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|                | Acoustic stimulation tests                  | 9                                                                       | 9          | 1           | 3          | 12                | 0                                                              | 0          |
|                | Acoustic stimulation tests abnormal         | 11                                                                      | 13         | 0           | 1          | 14                | 0                                                              | 0          |
|                | Acoustic stimulation tests normal           | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                | Activated partial thromboplastin time       | 6                                                                       | 6          | 3           | 4          | 10                | 0                                                              | 0          |
|                | Activated partial thromboplastin time abno  | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|                | Activated partial thromboplastin time norm  | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                | Activated partial thromboplastin time prolo | 4                                                                       | 4          | 1           | 3          | 7                 | 0                                                              | 0          |
|                | Activated partial thromboplastin time short | 3                                                                       | 4          | 1           | 1          | 5                 | 0                                                              | 0          |
|                | Adenovirus test                             | 11                                                                      | 11         | 1           | 1          | 12                | 0                                                              | 0          |
|                | Adenovirus test positive                    | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                | Alanine aminotransferase                    | 3                                                                       | 3          | 0           | 1          | 4                 | 0                                                              | 0          |
|                | Alanine aminotransferase decreased          | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|                | Alanine aminotransferase increased          | 31                                                                      | 38         | 11          | 22         | 60                | 0                                                              | 0          |
|                | Alanine aminotransferase normal             | 29                                                                      | 29         | 1           | 1          | 30                | 0                                                              | 0          |
|                | Albumin CSF decreased                       | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                | Albumin globulin ratio                      | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|                | Albumin globulin ratio normal               | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|                | Albumin urine present                       | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                | Alcohol test negative                       | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|                | Aldolase                                    | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|                | Allergy test                                | 1                                                                       | 1          | 3           | 4          | 5                 | 0                                                              | 0          |
|                | Allergy test negative                       | 2                                                                       | 2          | 1           | 1          | 3                 | 0                                                              | 0          |
|                | Allergy test positive                       | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|                | Amino acid level normal                     | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                | Ammonia                                     | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                | Ammonia decreased                           | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                | Ammonia increased                           | 1                                                                       | 2          | 0           | 1          | 3                 | 0                                                              | 0          |
|                | Ammonia normal                              | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                | Amniotic fluid index decreased              | 2                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|                | Amniotic fluid volume increased             | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                | Amniotic membrane rupture test positive     | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                | Amphetamines negative                       | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                | Amylase                                     | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|                | Amylase increased                           | 1                                                                       | 1          | 1           | 3          | 4                 | 0                                                              | 0          |

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|----------|-----------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                               | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                            | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Analgesic drug level                          | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Analgesic drug level increased                | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Angiocardiogram                               | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Angiogram                                     | 30                                                                      | 30         | 8           | 10         | 40                | 0                                                              | 0          |
|          | Angiogram abnormal                            | 7                                                                       | 10         | 1           | 1          | 11                | 0                                                              | 0          |
|          | Angiogram cerebral                            | 9                                                                       | 9          | 0           | 0          | 9                 | 0                                                              | 0          |
|          | Angiogram cerebral abnormal                   | 8                                                                       | 9          | 0           | 0          | 9                 | 0                                                              | 0          |
|          | Angiogram cerebral normal                     | 8                                                                       | 8          | 0           | 0          | 8                 | 0                                                              | 0          |
|          | Angiogram normal                              | 11                                                                      | 11         | 0           | 0          | 11                | 0                                                              | 0          |
|          | Angiogram peripheral abnormal                 | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Angiogram pulmonary                           | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Angiogram pulmonary abnormal                  | 48                                                                      | 50         | 0           | 1          | 51                | 0                                                              | 0          |
|          | Angiogram pulmonary normal                    | 12                                                                      | 12         | 0           | 0          | 12                | 0                                                              | 0          |
|          | Angiotensin converting enzyme                 | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Anion gap                                     | 30                                                                      | 30         | 1           | 2          | 32                | 0                                                              | 0          |
|          | Anion gap decreased                           | 6                                                                       | 6          | 2           | 2          | 8                 | 0                                                              | 0          |
|          | Anion gap increased                           | 4                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Anion gap normal                              | 9                                                                       | 9          | 1           | 1          | 10                | 0                                                              | 0          |
|          | Ankle brachial index abnormal                 | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Ankle brachial index decreased                | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Anti factor VIII antibody positive            | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Anti-GAD antibody positive                    | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Anti-RNA polymerase III antibody              | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Anti-cyclic citrullinated peptide antibody    | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Anti-cyclic citrullinated peptide antibody ne | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Anti-cyclic citrullinated peptide antibody po | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Anti-platelet antibody positive               | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Anti-thrombin antibody                        | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Anti-thyroid antibody                         | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Anti-thyroid antibody decreased               | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Anti-thyroid antibody increased               | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Anti-thyroid antibody positive                | 4                                                                       | 4          | 1           | 1          | 5                 | 0                                                              | 0          |
|          | Anti-transglutaminase antibody                | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Antiacyetylcholine receptor antibody          | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Antiacyetylcholine receptor antibody positiv  | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Antibiotic level                              | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Antibody test                                 | 3                                                                       | 3          | 1           | 4          | 7                 | 0                                                              | 0          |
|          | Antibody test abnormal                        | 0                                                                       | 0          | 1           | 9          | 9                 | 0                                                              | 0          |
|          | Antibody test negative                        | 0                                                                       | 0          | 5           | 45         | 45                | 0                                                              | 0          |
|          | Antibody test normal                          | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Antibody test positive                        | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Anticoagulation drug level above therapeutic  | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Anticoagulation drug level below therapeutic  | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Anticoagulation drug level therapeutic        | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Anticonvulsant drug level                     | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Antimicrobial susceptibility test             | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Antimitochondrial antibody                    | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Antimitochondrial antibody positive           | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Antineutrophil cytoplasmic antibody           | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |



|          |                                              | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|----------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                              | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                           | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Antineutrophil cytoplasmic antibody positive | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Antinuclear antibody                         | 6                                                                       | 6          | 3           | 5          | 11                | 0                                                              | 0          |
|          | Antinuclear antibody increased               | 0                                                                       | 0          | 2           | 2          | 2                 | 0                                                              | 0          |
|          | Antinuclear antibody negative                | 9                                                                       | 9          | 1           | 2          | 11                | 0                                                              | 0          |
|          | Antinuclear antibody positive                | 6                                                                       | 6          | 5           | 6          | 12                | 0                                                              | 0          |
|          | Antiphospholipid antibodies                  | 4                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Antiphospholipid antibodies negative         | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Antiphospholipid antibodies positive         | 2                                                                       | 2          | 0           | 1          | 3                 | 0                                                              | 0          |
|          | Antipsychotic drug level below therapeutic   | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Antithrombin III                             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Antral follicle count low                    | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Arteriogram carotid                          | 10                                                                      | 10         | 0           | 1          | 11                | 0                                                              | 0          |
|          | Arteriogram carotid abnormal                 | 5                                                                       | 6          | 0           | 0          | 6                 | 0                                                              | 0          |
|          | Arteriogram carotid normal                   | 5                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Arteriogram coronary abnormal                | 7                                                                       | 8          | 0           | 0          | 8                 | 0                                                              | 0          |
|          | Arteriogram coronary normal                  | 3                                                                       | 3          | 0           | 1          | 4                 | 0                                                              | 0          |
|          | Aspartate aminotransferase                   | 2                                                                       | 2          | 1           | 1          | 3                 | 0                                                              | 0          |
|          | Aspartate aminotransferase decreased         | 1                                                                       | 2          | 0           | 1          | 3                 | 0                                                              | 0          |
|          | Aspartate aminotransferase increased         | 33                                                                      | 40         | 5           | 14         | 54                | 0                                                              | 0          |
|          | Aspartate aminotransferase normal            | 21                                                                      | 21         | 2           | 2          | 23                | 0                                                              | 0          |
|          | Aspergillus test                             | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Aspergillus test positive                    | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Aspiration bursa                             | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Aspiration joint                             | 1                                                                       | 2          | 0           | 1          | 3                 | 0                                                              | 0          |
|          | Aspiration pleural cavity                    | 4                                                                       | 6          | 0           | 1          | 7                 | 0                                                              | 0          |
|          | Astrovirus test                              | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Atrial natriuretic peptide normal            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Atrial pressure increased                    | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Audiogram                                    | 2                                                                       | 2          | 0           | 3          | 5                 | 0                                                              | 0          |
|          | Audiogram abnormal                           | 9                                                                       | 9          | 0           | 2          | 11                | 0                                                              | 0          |
|          | Audiogram normal                             | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Auscultation                                 | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Autoantibody positive                        | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|          | Autoantibody test                            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Autopsy                                      | 7                                                                       | 8          | 0           | 0          | 8                 | 0                                                              | 0          |
|          | B-lymphocyte count decreased                 | 0                                                                       | 0          | 2           | 2          | 2                 | 0                                                              | 0          |
|          | Babinski reflex test                         | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Bacterial test                               | 7                                                                       | 7          | 3           | 3          | 10                | 0                                                              | 0          |
|          | Bacterial test negative                      | 4                                                                       | 4          | 0           | 1          | 5                 | 0                                                              | 0          |
|          | Bacterial test positive                      | 5                                                                       | 5          | 0           | 3          | 8                 | 0                                                              | 0          |
|          | Bacteroides test positive                    | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Balance test                                 | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Band neutrophil count                        | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Band neutrophil percentage                   | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Band neutrophil percentage increased         | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Barbiturates negative                        | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Barium swallow                               | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Barium swallow normal                        | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Base excess                                  | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |

|          |                                       | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|---------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                       | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                    | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Base excess increased                 | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Basophil count                        | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Basophil count abnormal               | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Basophil count decreased              | 8                                                                       | 8          | 0           | 0          | 8                 | 0                                                              | 0          |
|          | Basophil count normal                 | 6                                                                       | 6          | 0           | 0          | 6                 | 0                                                              | 0          |
|          | Basophil percentage                   | 10                                                                      | 10         | 1           | 1          | 11                | 0                                                              | 0          |
|          | Basophil percentage decreased         | 22                                                                      | 22         | 0           | 0          | 22                | 0                                                              | 0          |
|          | Basophil percentage increased         | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Beta-2 glycoprotein antibody          | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Beta-2 glycoprotein antibody negative | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Beta-2 glycoprotein antibody positive | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Bile output                           | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Bile output abnormal                  | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Bilirubin conjugated                  | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Bilirubin conjugated increased        | 3                                                                       | 3          | 0           | 1          | 4                 | 0                                                              | 0          |
|          | Bilirubin urine                       | 5                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Biopsy                                | 6                                                                       | 6          | 3           | 6          | 12                | 0                                                              | 0          |
|          | Biopsy artery                         | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Biopsy artery abnormal                | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Biopsy artery normal                  | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Biopsy bone marrow                    | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Biopsy bone marrow abnormal           | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Biopsy brain                          | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Biopsy breast                         | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Biopsy breast abnormal                | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Biopsy chorionic villous abnormal     | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Biopsy endometrium normal             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Biopsy intestine normal               | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Biopsy kidney                         | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Biopsy kidney abnormal                | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Biopsy liver                          | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Biopsy liver abnormal                 | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Biopsy lung                           | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Biopsy lung abnormal                  | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Biopsy lymph gland                    | 3                                                                       | 3          | 0           | 2          | 5                 | 0                                                              | 0          |
|          | Biopsy muscle                         | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Biopsy muscle normal                  | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Biopsy oesophagus abnormal            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Biopsy peripheral nerve               | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Biopsy salivary gland abnormal        | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Biopsy skin                           | 4                                                                       | 5          | 1           | 2          | 7                 | 0                                                              | 0          |
|          | Biopsy skin abnormal                  | 6                                                                       | 6          | 2           | 3          | 9                 | 0                                                              | 0          |
|          | Biopsy skin normal                    | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|          | Biopsy soft tissue                    | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Biopsy stomach                        | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Bladder scan                          | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Blast cells present                   | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Bleeding time                         | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Bleeding time abnormal                | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |

|          |                                          | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                          | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                       | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Bleeding time prolonged                  | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|          | Blood albumin                            | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Blood albumin decreased                  | 26                                                                      | 26         | 1           | 2          | 28                | 0                                                              | 0          |
|          | Blood albumin increased                  | 2                                                                       | 2          | 0           | 1          | 3                 | 0                                                              | 0          |
|          | Blood albumin normal                     | 11                                                                      | 11         | 1           | 2          | 13                | 0                                                              | 0          |
|          | Blood alcohol increased                  | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Blood aldosterone decreased              | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Blood alkaline phosphatase               | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Blood alkaline phosphatase decreased     | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Blood alkaline phosphatase increased     | 15                                                                      | 19         | 2           | 5          | 24                | 0                                                              | 0          |
|          | Blood alkaline phosphatase normal        | 28                                                                      | 28         | 2           | 2          | 30                | 0                                                              | 0          |
|          | Blood beta-D-glucan abnormal             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Blood bicarbonate                        | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Blood bicarbonate decreased              | 10                                                                      | 10         | 0           | 0          | 10                | 0                                                              | 0          |
|          | Blood bicarbonate increased              | 5                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Blood bicarbonate normal                 | 12                                                                      | 12         | 0           | 0          | 12                | 0                                                              | 0          |
|          | Blood bilirubin                          | 2                                                                       | 2          | 1           | 1          | 3                 | 0                                                              | 0          |
|          | Blood bilirubin decreased                | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Blood bilirubin increased                | 16                                                                      | 19         | 1           | 4          | 23                | 0                                                              | 0          |
|          | Blood bilirubin normal                   | 32                                                                      | 32         | 2           | 3          | 35                | 0                                                              | 0          |
|          | Blood calcitonin increased               | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Blood calcium                            | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Blood calcium decreased                  | 28                                                                      | 29         | 2           | 4          | 33                | 0                                                              | 0          |
|          | Blood calcium increased                  | 2                                                                       | 2          | 1           | 1          | 3                 | 0                                                              | 0          |
|          | Blood calcium normal                     | 17                                                                      | 17         | 1           | 2          | 19                | 0                                                              | 0          |
|          | Blood catecholamines                     | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Blood chloride                           | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Blood chloride decreased                 | 17                                                                      | 17         | 0           | 2          | 19                | 0                                                              | 0          |
|          | Blood chloride increased                 | 15                                                                      | 16         | 1           | 2          | 18                | 0                                                              | 0          |
|          | Blood chloride normal                    | 28                                                                      | 28         | 2           | 3          | 31                | 0                                                              | 0          |
|          | Blood cholesterol abnormal               | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Blood cholesterol decreased              | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Blood cholesterol increased              | 6                                                                       | 7          | 6           | 20         | 27                | 0                                                              | 0          |
|          | Blood cholesterol normal                 | 3                                                                       | 3          | 1           | 3          | 6                 | 0                                                              | 0          |
|          | Blood copper normal                      | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Blood corticotrophin normal              | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Blood creatine                           | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Blood creatine increased                 | 3                                                                       | 3          | 1           | 1          | 4                 | 0                                                              | 0          |
|          | Blood creatine normal                    | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Blood creatine phosphokinase             | 4                                                                       | 5          | 0           | 3          | 8                 | 0                                                              | 0          |
|          | Blood creatine phosphokinase MB          | 4                                                                       | 4          | 1           | 1          | 5                 | 0                                                              | 0          |
|          | Blood creatine phosphokinase MB increase | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Blood creatine phosphokinase abnormal    | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Blood creatine phosphokinase decreased   | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Blood creatine phosphokinase increased   | 22                                                                      | 25         | 5           | 11         | 36                | 0                                                              | 0          |
|          | Blood creatine phosphokinase normal      | 9                                                                       | 9          | 1           | 2          | 11                | 0                                                              | 0          |
|          | Blood creatinine                         | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Blood creatinine abnormal                | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Blood creatinine decreased               | 2                                                                       | 2          | 1           | 1          | 3                 | 0                                                              | 0          |

|          |                                       | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|---------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                       | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                    | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Blood creatinine increased            | 83                                                                      | 90         | 6           | 12         | 102               | 0                                                              | 0          |
|          | Blood creatinine normal               | 36                                                                      | 36         | 4           | 6          | 42                | 0                                                              | 0          |
|          | Blood culture                         | 27                                                                      | 27         | 1           | 2          | 29                | 0                                                              | 0          |
|          | Blood culture negative                | 23                                                                      | 24         | 0           | 0          | 24                | 0                                                              | 0          |
|          | Blood culture positive                | 16                                                                      | 19         | 0           | 0          | 19                | 0                                                              | 0          |
|          | Blood electrolytes                    | 2                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Blood electrolytes abnormal           | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Blood electrolytes decreased          | 0                                                                       | 0          | 2           | 2          | 2                 | 0                                                              | 0          |
|          | Blood electrolytes normal             | 9                                                                       | 9          | 1           | 1          | 10                | 0                                                              | 0          |
|          | Blood erythropoietin increased        | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Blood erythropoietin normal           | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Blood fibrinogen                      | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Blood fibrinogen increased            | 7                                                                       | 9          | 1           | 1          | 10                | 0                                                              | 0          |
|          | Blood fibrinogen normal               | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Blood folate                          | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Blood folate decreased                | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Blood folate normal                   | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Blood follicle stimulating hormone    | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Blood gases                           | 14                                                                      | 14         | 1           | 2          | 16                | 0                                                              | 0          |
|          | Blood gases abnormal                  | 4                                                                       | 4          | 0           | 1          | 5                 | 0                                                              | 0          |
|          | Blood gases normal                    | 3                                                                       | 3          | 1           | 1          | 4                 | 0                                                              | 0          |
|          | Blood glucose                         | 6                                                                       | 6          | 2           | 14         | 20                | 0                                                              | 0          |
|          | Blood glucose abnormal                | 4                                                                       | 4          | 5           | 22         | 26                | 0                                                              | 0          |
|          | Blood glucose decreased               | 15                                                                      | 21         | 14          | 85         | 106               | 0                                                              | 0          |
|          | Blood glucose fluctuation             | 2                                                                       | 4          | 6           | 25         | 29                | 0                                                              | 0          |
|          | Blood glucose increased               | 56                                                                      | 85         | 33          | 286        | 371               | 0                                                              | 0          |
|          | Blood glucose normal                  | 52                                                                      | 53         | 6           | 14         | 67                | 0                                                              | 0          |
|          | Blood homocysteine increased          | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|          | Blood immunoglobulin E                | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Blood immunoglobulin G                | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Blood immunoglobulin G abnormal       | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Blood immunoglobulin G decreased      | 0                                                                       | 1          | 2           | 2          | 3                 | 0                                                              | 0          |
|          | Blood immunoglobulin G increased      | 1                                                                       | 1          | 1           | 2          | 3                 | 0                                                              | 0          |
|          | Blood immunoglobulin G normal         | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Blood immunoglobulin M                | 4                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Blood immunoglobulin M abnormal       | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Blood immunoglobulin M increased      | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Blood immunoglobulin M normal         | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Blood insulin abnormal                | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Blood insulin increased               | 0                                                                       | 0          | 1           | 3          | 3                 | 0                                                              | 0          |
|          | Blood iron                            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Blood iron decreased                  | 4                                                                       | 4          | 4           | 10         | 14                | 0                                                              | 0          |
|          | Blood iron increased                  | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|          | Blood iron normal                     | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Blood ketone body                     | 2                                                                       | 2          | 0           | 1          | 3                 | 0                                                              | 0          |
|          | Blood lactate dehydrogenase           | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Blood lactate dehydrogenase decreased | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Blood lactate dehydrogenase increased | 19                                                                      | 20         | 1           | 1          | 21                | 0                                                              | 0          |
|          | Blood lactate dehydrogenase normal    | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |

|          |                                      | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|--------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                      | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                   | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Blood lactic acid                    | 33                                                                      | 34         | 2           | 3          | 37                | 0                                                              | 0          |
|          | Blood lactic acid decreased          | 5                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Blood lactic acid increased          | 14                                                                      | 17         | 0           | 0          | 17                | 0                                                              | 0          |
|          | Blood lactic acid normal             | 9                                                                       | 9          | 0           | 0          | 9                 | 0                                                              | 0          |
|          | Blood magnesium                      | 13                                                                      | 13         | 5           | 6          | 19                | 0                                                              | 0          |
|          | Blood magnesium decreased            | 3                                                                       | 4          | 3           | 5          | 9                 | 0                                                              | 0          |
|          | Blood magnesium increased            | 5                                                                       | 5          | 0           | 1          | 6                 | 0                                                              | 0          |
|          | Blood magnesium normal               | 13                                                                      | 14         | 2           | 2          | 16                | 0                                                              | 0          |
|          | Blood methaemoglobin                 | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Blood oestrogen increased            | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|          | Blood osmolarity decreased           | 3                                                                       | 3          | 1           | 1          | 4                 | 0                                                              | 0          |
|          | Blood osmolarity increased           | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Blood osmolarity normal              | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Blood pH decreased                   | 8                                                                       | 8          | 0           | 0          | 8                 | 0                                                              | 0          |
|          | Blood pH normal                      | 5                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Blood parathyroid hormone            | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Blood parathyroid hormone abnormal   | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Blood phosphorus                     | 4                                                                       | 4          | 1           | 1          | 5                 | 0                                                              | 0          |
|          | Blood phosphorus decreased           | 7                                                                       | 7          | 0           | 0          | 7                 | 0                                                              | 0          |
|          | Blood phosphorus increased           | 4                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Blood phosphorus normal              | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Blood potassium                      | 4                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Blood potassium abnormal             | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Blood potassium decreased            | 28                                                                      | 40         | 10          | 19         | 59                | 0                                                              | 0          |
|          | Blood potassium increased            | 19                                                                      | 19         | 0           | 5          | 24                | 0                                                              | 0          |
|          | Blood potassium normal               | 42                                                                      | 42         | 3           | 4          | 46                | 0                                                              | 0          |
|          | Blood pressure abnormal              | 20                                                                      | 32         | 20          | 78         | 110               | 0                                                              | 0          |
|          | Blood pressure ambulatory decreased  | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Blood pressure ambulatory increased  | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Blood pressure decreased             | 75                                                                      | 116        | 162         | 335        | 451               | 0                                                              | 0          |
|          | Blood pressure diastolic decreased   | 0                                                                       | 0          | 2           | 3          | 3                 | 0                                                              | 0          |
|          | Blood pressure diastolic increased   | 4                                                                       | 6          | 5           | 11         | 17                | 0                                                              | 0          |
|          | Blood pressure immeasurable          | 2                                                                       | 2          | 1           | 2          | 4                 | 0                                                              | 0          |
|          | Blood pressure increased             | 194                                                                     | 322        | 1210        | 2029       | 2351              | 0                                                              | 0          |
|          | Blood pressure measurement           | 7                                                                       | 7          | 3           | 25         | 32                | 0                                                              | 0          |
|          | Blood pressure normal                | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Blood pressure orthostatic           | 1                                                                       | 1          | 1           | 4          | 5                 | 0                                                              | 0          |
|          | Blood pressure orthostatic abnormal  | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Blood pressure orthostatic decreased | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Blood pressure systolic abnormal     | 0                                                                       | 0          | 1           | 3          | 3                 | 0                                                              | 0          |
|          | Blood pressure systolic decreased    | 0                                                                       | 1          | 5           | 7          | 8                 | 0                                                              | 0          |
|          | Blood pressure systolic increased    | 1                                                                       | 4          | 4           | 11         | 15                | 0                                                              | 0          |
|          | Blood prolactin increased            | 0                                                                       | 0          | 3           | 3          | 3                 | 0                                                              | 0          |
|          | Blood smear test                     | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Blood smear test abnormal            | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Blood smear test normal              | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Blood sodium                         | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Blood sodium abnormal                | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Blood sodium decreased               | 40                                                                      | 46         | 4           | 10         | 56                | 0                                                              | 0          |

|          |                                                | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|------------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                                | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                             | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Blood sodium increased                         | 4                                                                       | 5          | 0           | 1          | 6                 | 0                                                              | 0          |
|          | Blood sodium normal                            | 39                                                                      | 40         | 3           | 4          | 44                | 0                                                              | 0          |
|          | Blood test                                     | 195                                                                     | 196        | 117         | 147        | 343               | 0                                                              | 0          |
|          | Blood test abnormal                            | 35                                                                      | 38         | 17          | 29         | 67                | 0                                                              | 0          |
|          | Blood test normal                              | 45                                                                      | 45         | 31          | 35         | 80                | 0                                                              | 0          |
|          | Blood testosterone decreased                   | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Blood testosterone increased                   | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Blood testosterone normal                      | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Blood thromboplastin decreased                 | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Blood thyroid stimulating hormone              | 10                                                                      | 10         | 10          | 12         | 22                | 0                                                              | 0          |
|          | Blood thyroid stimulating hormone abnormal     | 1                                                                       | 1          | 4           | 4          | 5                 | 0                                                              | 0          |
|          | Blood thyroid stimulating hormone decreased    | 9                                                                       | 10         | 7           | 10         | 20                | 0                                                              | 0          |
|          | Blood thyroid stimulating hormone increased    | 10                                                                      | 10         | 7           | 12         | 22                | 0                                                              | 0          |
|          | Blood thyroid stimulating hormone normal       | 10                                                                      | 10         | 3           | 3          | 13                | 0                                                              | 0          |
|          | Blood triglycerides                            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Blood triglycerides decreased                  | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Blood triglycerides increased                  | 1                                                                       | 2          | 1           | 2          | 4                 | 0                                                              | 0          |
|          | Blood triglycerides normal                     | 2                                                                       | 2          | 0           | 2          | 4                 | 0                                                              | 0          |
|          | Blood urea                                     | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Blood urea decreased                           | 1                                                                       | 1          | 2           | 4          | 5                 | 0                                                              | 0          |
|          | Blood urea increased                           | 47                                                                      | 52         | 0           | 1          | 53                | 0                                                              | 0          |
|          | Blood urea nitrogen/creatinine ratio           | 6                                                                       | 6          | 1           | 2          | 8                 | 0                                                              | 0          |
|          | Blood urea nitrogen/creatinine ratio increased | 4                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Blood urea normal                              | 29                                                                      | 29         | 2           | 3          | 32                | 0                                                              | 0          |
|          | Blood uric acid                                | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|          | Blood uric acid increased                      | 2                                                                       | 2          | 0           | 3          | 5                 | 0                                                              | 0          |
|          | Blood uric acid normal                         | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Blood urine                                    | 5                                                                       | 6          | 4           | 9          | 15                | 0                                                              | 0          |
|          | Blood urine absent                             | 4                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Blood urine present                            | 28                                                                      | 34         | 37          | 130        | 164               | 0                                                              | 0          |
|          | Blood viscosity increased                      | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Blood zinc abnormal                            | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Blood zinc decreased                           | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Body height                                    | 0                                                                       | 0          | 0           | 4          | 4                 | 0                                                              | 0          |
|          | Body mass index                                | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Body temperature                               | 56                                                                      | 58         | 28          | 72         | 130               | 0                                                              | 0          |
|          | Body temperature abnormal                      | 6                                                                       | 8          | 19          | 52         | 60                | 0                                                              | 0          |
|          | Body temperature decreased                     | 19                                                                      | 20         | 27          | 100        | 120               | 0                                                              | 0          |
|          | Body temperature fluctuation                   | 19                                                                      | 21         | 20          | 70         | 91                | 0                                                              | 0          |
|          | Body temperature increased                     | 113                                                                     | 165        | 917         | 2409       | 2574              | 0                                                              | 0          |
|          | Body temperature normal                        | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Bone density decreased                         | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Bone scan                                      | 2                                                                       | 2          | 1           | 1          | 3                 | 0                                                              | 0          |
|          | Bordetella test                                | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Bordetella test negative                       | 10                                                                      | 10         | 1           | 1          | 11                | 0                                                              | 0          |
|          | Borrelia test                                  | 2                                                                       | 2          | 1           | 1          | 3                 | 0                                                              | 0          |
|          | Borrelia test negative                         | 3                                                                       | 3          | 1           | 1          | 4                 | 0                                                              | 0          |
|          | Borrelia test positive                         | 5                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Brachial pulse decreased                       | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |

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|----------|--------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                      | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                   | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Brain natriuretic peptide            | 9                                                                       | 9          | 1           | 1          | 10                | 0                                                              | 0          |
|          | Brain natriuretic peptide increased  | 33                                                                      | 37         | 4           | 7          | 44                | 0                                                              | 0          |
|          | Brain natriuretic peptide normal     | 15                                                                      | 16         | 1           | 1          | 17                | 0                                                              | 0          |
|          | Brain scan abnormal                  | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Brain scan normal                    | 3                                                                       | 3          | 3           | 3          | 6                 | 0                                                              | 0          |
|          | Breath sounds                        | 1                                                                       | 1          | 1           | 3          | 4                 | 0                                                              | 0          |
|          | Breath sounds abnormal               | 8                                                                       | 12         | 2           | 15         | 27                | 0                                                              | 0          |
|          | Breath sounds absent                 | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Breath sounds normal                 | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Bronchoalveolar lavage               | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Bronchoalveolar lavage abnormal      | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Bronchoalveolar lavage normal        | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Bronchoscopy                         | 2                                                                       | 2          | 1           | 1          | 3                 | 0                                                              | 0          |
|          | Bronchoscopy abnormal                | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Bronchoscopy normal                  | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | C-reactive protein                   | 25                                                                      | 26         | 9           | 13         | 39                | 0                                                              | 0          |
|          | C-reactive protein abnormal          | 2                                                                       | 2          | 2           | 2          | 4                 | 0                                                              | 0          |
|          | C-reactive protein decreased         | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | C-reactive protein increased         | 115                                                                     | 124        | 44          | 56         | 180               | 0                                                              | 0          |
|          | C-reactive protein normal            | 9                                                                       | 9          | 2           | 2          | 11                | 0                                                              | 0          |
|          | CD4 lymphocytes decreased            | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | CHA2DS2-VASc-score                   | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | CSF culture                          | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | CSF culture negative                 | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | CSF glucose decreased                | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | CSF glucose increased                | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | CSF glucose normal                   | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | CSF immunoglobulin G index           | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | CSF mononuclear cell count increased | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | CSF oligoclonal band present         | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | CSF pressure increased               | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | CSF protein increased                | 6                                                                       | 10         | 0           | 1          | 11                | 0                                                              | 0          |
|          | CSF red blood cell count             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | CSF red blood cell count positive    | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | CSF test                             | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | CSF test abnormal                    | 2                                                                       | 2          | 1           | 1          | 3                 | 0                                                              | 0          |
|          | CSF volume                           | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | CSF white blood cell count increased | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | CSF white blood cell count negative  | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Calcium ionised increased            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Campylobacter test                   | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Capillary permeability increased     | 1                                                                       | 3          | 1           | 1          | 4                 | 0                                                              | 0          |
|          | Carbohydrate antigen 125 normal      | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Carbohydrate antigen 15-3 increased  | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Carbohydrate antigen 19-9 increased  | 0                                                                       | 0          | 2           | 2          | 2                 | 0                                                              | 0          |
|          | Carbohydrate antigen 27.29 increased | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Carbon dioxide                       | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Carbon dioxide decreased             | 10                                                                      | 10         | 0           | 1          | 11                | 0                                                              | 0          |
|          | Carbon dioxide increased             | 5                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |

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|----------|---------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                       | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                    | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Carbon dioxide normal                 | 21                                                                      | 21         | 2           | 3          | 24                | 0                                                              | 0          |
|          | Carboxyhaemoglobin                    | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Carboxyhaemoglobin normal             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Carcinoembryonic antigen increased    | 0                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Cardiac function test                 | 2                                                                       | 2          | 1           | 2          | 4                 | 0                                                              | 0          |
|          | Cardiac function test abnormal        | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Cardiac function test normal          | 3                                                                       | 3          | 1           | 1          | 4                 | 0                                                              | 0          |
|          | Cardiac imaging procedure             | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Cardiac imaging procedure abnormal    | 12                                                                      | 12         | 0           | 1          | 13                | 0                                                              | 0          |
|          | Cardiac imaging procedure normal      | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Cardiac index decreased               | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Cardiac monitoring                    | 21                                                                      | 22         | 22          | 28         | 50                | 0                                                              | 0          |
|          | Cardiac monitoring abnormal           | 7                                                                       | 8          | 6           | 6          | 14                | 0                                                              | 0          |
|          | Cardiac monitoring normal             | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Cardiac murmur                        | 13                                                                      | 18         | 12          | 18         | 36                | 0                                                              | 0          |
|          | Cardiac output increased              | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Cardiac pharmacologic stress test     | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Cardiac stress test                   | 26                                                                      | 27         | 22          | 23         | 50                | 0                                                              | 0          |
|          | Cardiac stress test abnormal          | 6                                                                       | 6          | 2           | 2          | 8                 | 0                                                              | 0          |
|          | Cardiac stress test normal            | 3                                                                       | 3          | 6           | 6          | 9                 | 0                                                              | 0          |
|          | Cardiac telemetry                     | 9                                                                       | 9          | 1           | 1          | 10                | 0                                                              | 0          |
|          | Cardiac telemetry abnormal            | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Cardiac telemetry normal              | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Cardiac ventriculogram left           | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Cardiolipin antibody                  | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Cardiolipin antibody negative         | 2                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Cardiolipin antibody positive         | 3                                                                       | 3          | 0           | 1          | 4                 | 0                                                              | 0          |
|          | Cardiovascular evaluation             | 4                                                                       | 7          | 0           | 2          | 9                 | 0                                                              | 0          |
|          | Cardiovascular function test abnormal | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Carotid pulse                         | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Carotid pulse abnormal                | 1                                                                       | 2          | 1           | 1          | 3                 | 0                                                              | 0          |
|          | Catheter culture positive             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Catheterisation cardiac               | 27                                                                      | 35         | 3           | 6          | 41                | 0                                                              | 0          |
|          | Catheterisation cardiac abnormal      | 15                                                                      | 18         | 0           | 0          | 18                | 0                                                              | 0          |
|          | Catheterisation cardiac normal        | 12                                                                      | 12         | 0           | 0          | 12                | 0                                                              | 0          |
|          | Central venous pressure abnormal      | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Ceruloplasmin                         | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Chest X-ray                           | 97                                                                      | 98         | 48          | 60         | 158               | 0                                                              | 0          |
|          | Chest X-ray abnormal                  | 238                                                                     | 246        | 14          | 16         | 262               | 0                                                              | 0          |
|          | Chest X-ray normal                    | 74                                                                      | 74         | 21          | 27         | 101               | 0                                                              | 0          |
|          | Chest scan                            | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Chlamydia test negative               | 9                                                                       | 9          | 1           | 1          | 10                | 0                                                              | 0          |
|          | Chlamydia test positive               | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Clostridium test                      | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Clostridium test negative             | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Clostridium test positive             | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Coagulation factor                    | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Coagulation test                      | 4                                                                       | 5          | 0           | 1          | 6                 | 0                                                              | 0          |
|          | Coagulation test abnormal             | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |



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|          |                                        | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                     | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Coagulation test normal                | 5                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Coagulation time                       | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Coagulation time abnormal              | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Coagulation time prolonged             | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Coagulation time shortened             | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Cognitive test                         | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Colonoscopy                            | 4                                                                       | 4          | 1           | 3          | 7                 | 0                                                              | 0          |
|          | Colonoscopy abnormal                   | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Colonoscopy normal                     | 6                                                                       | 6          | 1           | 1          | 7                 | 0                                                              | 0          |
|          | Coma scale                             | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Coma scale abnormal                    | 0                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Complement factor                      | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Complement factor C3                   | 1                                                                       | 2          | 1           | 1          | 3                 | 0                                                              | 0          |
|          | Complement factor C4                   | 1                                                                       | 2          | 1           | 1          | 3                 | 0                                                              | 0          |
|          | Computerised tomogram                  | 139                                                                     | 141        | 50          | 59         | 200               | 0                                                              | 0          |
|          | Computerised tomogram abdomen          | 12                                                                      | 12         | 3           | 4          | 16                | 0                                                              | 0          |
|          | Computerised tomogram abdomen abnormal | 49                                                                      | 51         | 3           | 4          | 55                | 0                                                              | 0          |
|          | Computerised tomogram abdomen normal   | 7                                                                       | 7          | 2           | 2          | 9                 | 0                                                              | 0          |
|          | Computerised tomogram abnormal         | 27                                                                      | 35         | 13          | 15         | 50                | 0                                                              | 0          |
|          | Computerised tomogram coronary artery  | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Computerised tomogram head             | 40                                                                      | 41         | 19          | 20         | 61                | 0                                                              | 0          |
|          | Computerised tomogram head abnormal    | 40                                                                      | 42         | 0           | 0          | 42                | 0                                                              | 0          |
|          | Computerised tomogram head normal      | 54                                                                      | 54         | 4           | 5          | 59                | 0                                                              | 0          |
|          | Computerised tomogram neck             | 11                                                                      | 11         | 2           | 2          | 13                | 0                                                              | 0          |
|          | Computerised tomogram normal           | 31                                                                      | 31         | 14          | 19         | 50                | 0                                                              | 0          |
|          | Computerised tomogram pelvis           | 3                                                                       | 3          | 1           | 1          | 4                 | 0                                                              | 0          |
|          | Computerised tomogram pelvis abnormal  | 0                                                                       | 1          | 1           | 2          | 3                 | 0                                                              | 0          |
|          | Computerised tomogram spine            | 12                                                                      | 13         | 0           | 0          | 13                | 0                                                              | 0          |
|          | Computerised tomogram thorax           | 36                                                                      | 36         | 2           | 4          | 40                | 0                                                              | 0          |
|          | Computerised tomogram thorax abnormal  | 96                                                                      | 98         | 0           | 1          | 99                | 0                                                              | 0          |
|          | Computerised tomogram thorax normal    | 18                                                                      | 18         | 4           | 4          | 22                | 0                                                              | 0          |
|          | Continuous glucose monitoring          | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Coombs direct test                     | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Corneal reflex decreased               | 1                                                                       | 4          | 4           | 12         | 16                | 0                                                              | 0          |
|          | Coronavirus test negative              | 7                                                                       | 7          | 0           | 0          | 7                 | 0                                                              | 0          |
|          | Coronavirus test positive              | 8                                                                       | 9          | 3           | 12         | 21                | 0                                                              | 0          |
|          | Cortisol free urine normal             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Cortisol increased                     | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Cortisol normal                        | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Coxsackie virus test                   | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Coxsackie virus test negative          | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Creatinine renal clearance             | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Creatinine renal clearance decreased   | 4                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Creatinine renal clearance increased   | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Creatinine urine normal                | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Cryoglobulins                          | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Cryoglobulins present                  | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Culture                                | 3                                                                       | 3          | 0           | 3          | 6                 | 0                                                              | 0          |
|          | Culture negative                       | 4                                                                       | 4          | 0           | 1          | 5                 | 0                                                              | 0          |

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|----------|----------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                              | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                           | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Culture positive                             | 5                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Culture stool                                | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Culture stool positive                       | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Culture urine                                | 8                                                                       | 8          | 0           | 3          | 11                | 0                                                              | 0          |
|          | Culture urine negative                       | 9                                                                       | 9          | 0           | 0          | 9                 | 0                                                              | 0          |
|          | Culture urine positive                       | 10                                                                      | 10         | 1           | 1          | 11                | 0                                                              | 0          |
|          | Culture wound                                | 1                                                                       | 1          | 0           | 2          | 3                 | 0                                                              | 0          |
|          | Culture wound negative                       | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Culture wound positive                       | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Cystogram                                    | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Cystoscopy                                   | 4                                                                       | 4          | 0           | 1          | 5                 | 0                                                              | 0          |
|          | Cytogenetic analysis                         | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Cytokine increased                           | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Cytology normal                              | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Cytomegalovirus test negative                | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Cytomegalovirus test positive                | 2                                                                       | 3          | 1           | 1          | 4                 | 0                                                              | 0          |
|          | Dental examination abnormal                  | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Dermatologic examination                     | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Diagnostic procedure                         | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Differential white blood cell count          | 43                                                                      | 43         | 10          | 12         | 55                | 0                                                              | 0          |
|          | Differential white blood cell count abnormal | 5                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Differential white blood cell count normal   | 3                                                                       | 3          | 1           | 2          | 5                 | 0                                                              | 0          |
|          | Digestive enzyme normal                      | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Discogram abnormal                           | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Double stranded DNA antibody                 | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Drug level abnormal                          | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Drug level changed                           | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Drug level decreased                         | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|          | Drug screen                                  | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Drug screen negative                         | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Drug screen positive                         | 1                                                                       | 1          | 2           | 2          | 3                 | 0                                                              | 0          |
|          | Drug specific antibody                       | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Drug specific antibody absent                | 0                                                                       | 0          | 0           | 5          | 5                 | 0                                                              | 0          |
|          | ECG signs of myocardial ischaemia            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Ear, nose and throat examination             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Ear, nose and throat examination abnormal    | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Ear, nose and throat examination normal      | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Echocardiogram                               | 137                                                                     | 139        | 50          | 55         | 194               | 0                                                              | 0          |
|          | Echocardiogram abnormal                      | 73                                                                      | 76         | 8           | 9          | 85                | 0                                                              | 0          |
|          | Echocardiogram normal                        | 35                                                                      | 35         | 8           | 9          | 44                | 0                                                              | 0          |
|          | Ejection fraction                            | 11                                                                      | 13         | 1           | 1          | 14                | 0                                                              | 0          |
|          | Ejection fraction decreased                  | 52                                                                      | 62         | 4           | 4          | 66                | 0                                                              | 0          |
|          | Ejection fraction normal                     | 20                                                                      | 20         | 0           | 0          | 20                | 0                                                              | 0          |
|          | Electrocardiogram                            | 114                                                                     | 114        | 123         | 158        | 272               | 0                                                              | 0          |
|          | Electrocardiogram J wave abnormal            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Electrocardiogram PR interval                | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Electrocardiogram PR segment depression      | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Electrocardiogram PR segment elevation       | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Electrocardiogram Q wave abnormal            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |

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|----------|-------------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                                 | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                              | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Electrocardiogram QRS complex                   | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Electrocardiogram QRS complex abnormal          | 3                                                                       | 3          | 1           | 2          | 5                 | 0                                                              | 0          |
|          | Electrocardiogram QRS complex normal            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Electrocardiogram QT interval                   | 7                                                                       | 7          | 1           | 1          | 8                 | 0                                                              | 0          |
|          | Electrocardiogram QT prolonged                  | 11                                                                      | 12         | 1           | 1          | 13                | 0                                                              | 0          |
|          | Electrocardiogram ST segment abnormal           | 2                                                                       | 2          | 1           | 1          | 3                 | 0                                                              | 0          |
|          | Electrocardiogram ST segment depression         | 2                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Electrocardiogram ST segment elevation          | 32                                                                      | 37         | 2           | 2          | 39                | 0                                                              | 0          |
|          | Electrocardiogram ST-T change                   | 7                                                                       | 7          | 0           | 0          | 7                 | 0                                                              | 0          |
|          | Electrocardiogram ST-T segment abnormal         | 2                                                                       | 3          | 1           | 1          | 4                 | 0                                                              | 0          |
|          | Electrocardiogram T wave abnormal               | 4                                                                       | 4          | 3           | 4          | 8                 | 0                                                              | 0          |
|          | Electrocardiogram T wave inversion              | 7                                                                       | 9          | 1           | 1          | 10                | 0                                                              | 0          |
|          | Electrocardiogram T wave normal                 | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Electrocardiogram T wave peaked                 | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Electrocardiogram abnormal                      | 94                                                                      | 105        | 65          | 74         | 179               | 0                                                              | 0          |
|          | Electrocardiogram ambulatory                    | 13                                                                      | 13         | 27          | 29         | 42                | 0                                                              | 0          |
|          | Electrocardiogram ambulatory abnormal           | 3                                                                       | 3          | 6           | 6          | 9                 | 0                                                              | 0          |
|          | Electrocardiogram ambulatory normal             | 4                                                                       | 4          | 1           | 1          | 5                 | 0                                                              | 0          |
|          | Electrocardiogram change                        | 3                                                                       | 3          | 1           | 1          | 4                 | 0                                                              | 0          |
|          | Electrocardiogram delta waves abnormal          | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Electrocardiogram normal                        | 64                                                                      | 64         | 38          | 51         | 115               | 0                                                              | 0          |
|          | Electrocardiogram repolarisation abnormal       | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Electroencephalogram                            | 22                                                                      | 23         | 6           | 7          | 30                | 0                                                              | 0          |
|          | Electroencephalogram abnormal                   | 7                                                                       | 7          | 3           | 4          | 11                | 0                                                              | 0          |
|          | Electroencephalogram normal                     | 9                                                                       | 9          | 1           | 1          | 10                | 0                                                              | 0          |
|          | Electromyogram                                  | 13                                                                      | 13         | 0           | 3          | 16                | 0                                                              | 0          |
|          | Electromyogram abnormal                         | 8                                                                       | 8          | 1           | 1          | 9                 | 0                                                              | 0          |
|          | Electromyogram normal                           | 3                                                                       | 3          | 1           | 1          | 4                 | 0                                                              | 0          |
|          | Electronystagmogram                             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Electronystagmogram abnormal                    | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Electronystagmogram normal                      | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Electrophoresis                                 | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Electrophoresis protein normal                  | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Emergency care examination                      | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|          | Emergency care examination normal               | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Endobronchial ultrasound                        | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Endocrine test normal                           | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Endoscopic retrograde cholangiopancreatography  | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Endoscopic retrograde cholangiopancreatography  | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Endoscopy                                       | 4                                                                       | 4          | 1           | 1          | 5                 | 0                                                              | 0          |
|          | Endoscopy gastrointestinal abnormal             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Endoscopy normal                                | 3                                                                       | 3          | 1           | 1          | 4                 | 0                                                              | 0          |
|          | Endoscopy upper gastrointestinal tract          | 1                                                                       | 1          | 1           | 2          | 3                 | 0                                                              | 0          |
|          | Endoscopy upper gastrointestinal tract abnormal | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Endoscopy upper gastrointestinal tract normal   | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Enterobacter test positive                      | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Enterococcus test positive                      | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Enterovirus test                                | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Enterovirus test negative                       | 10                                                                      | 10         | 1           | 1          | 11                | 0                                                              | 0          |

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|----------|-----------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                               | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                            | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Enterovirus test positive                     | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Enzyme level abnormal                         | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Enzyme level increased                        | 1                                                                       | 2          | 1           | 2          | 4                 | 0                                                              | 0          |
|          | Enzyme level test                             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Eosinophil count                              | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Eosinophil count decreased                    | 12                                                                      | 12         | 1           | 1          | 13                | 0                                                              | 0          |
|          | Eosinophil count increased                    | 3                                                                       | 3          | 2           | 7          | 10                | 0                                                              | 0          |
|          | Eosinophil count normal                       | 5                                                                       | 5          | 2           | 3          | 8                 | 0                                                              | 0          |
|          | Eosinophil percentage                         | 16                                                                      | 16         | 1           | 1          | 17                | 0                                                              | 0          |
|          | Eosinophil percentage decreased               | 19                                                                      | 19         | 1           | 2          | 21                | 0                                                              | 0          |
|          | Eosinophil percentage increased               | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Epinephrine increased                         | 0                                                                       | 0          | 0           | 3          | 3                 | 0                                                              | 0          |
|          | Epstein-Barr virus antibody                   | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Epstein-Barr virus antibody negative          | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Epstein-Barr virus antibody positive          | 1                                                                       | 2          | 1           | 2          | 4                 | 0                                                              | 0          |
|          | Epstein-Barr virus test                       | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Epstein-Barr virus test positive              | 2                                                                       | 2          | 3           | 4          | 6                 | 0                                                              | 0          |
|          | Erythrocyte osmotic fragility test            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Escherichia test negative                     | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Escherichia test positive                     | 4                                                                       | 4          | 1           | 1          | 5                 | 0                                                              | 0          |
|          | Exercise electrocardiogram                    | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Exercise test                                 | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Face and mouth X-ray normal                   | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Faecal calprotectin                           | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Faecal calprotectin increased                 | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Faecal volume increased                       | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | False negative pregnancy test                 | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | False positive radioisotope investigation res | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Fibrin D dimer                                | 66                                                                      | 68         | 11          | 12         | 80                | 0                                                              | 0          |
|          | Fibrin D dimer decreased                      | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Fibrin D dimer increased                      | 113                                                                     | 125        | 46          | 51         | 176               | 0                                                              | 0          |
|          | Fibrin D dimer normal                         | 9                                                                       | 9          | 7           | 7          | 16                | 0                                                              | 0          |
|          | Fibrin abnormal                               | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Flow cytometry                                | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Fluorescent in situ hybridisation             | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Foetal heart rate abnormal                    | 10                                                                      | 15         | 0           | 3          | 18                | 0                                                              | 0          |
|          | Foetal heart rate decreased                   | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Foetal heart rate increased                   | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Foetal non-stress test normal                 | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Forced expiratory volume decreased            | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Full blood count                              | 103                                                                     | 106        | 44          | 68         | 174               | 0                                                              | 0          |
|          | Full blood count abnormal                     | 20                                                                      | 25         | 13          | 19         | 44                | 0                                                              | 0          |
|          | Full blood count decreased                    | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Full blood count normal                       | 31                                                                      | 31         | 13          | 24         | 55                | 0                                                              | 0          |
|          | Functional residual capacity decreased        | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Fungal test                                   | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Fungal test negative                          | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Fungal test positive                          | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Gamma-glutamyltransferase increased           | 8                                                                       | 8          | 3           | 4          | 12                | 0                                                              | 0          |

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|          |                                            | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                         | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Gastric emptying study                     | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Gastric occult blood positive              | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Gastric pH decreased                       | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Gastrointestinal pathogen panel            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Gene mutation identification test          | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Gene mutation identification test negative | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Gene mutation identification test positive | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | General physical condition                 | 0                                                                       | 0          | 7           | 7          | 7                 | 0                                                              | 0          |
|          | General physical condition abnormal        | 11                                                                      | 13         | 4           | 10         | 23                | 0                                                              | 0          |
|          | General physical condition normal          | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Geriatric assessment                       | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Giardia test negative                      | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Globulin                                   | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Globulins decreased                        | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Globulins increased                        | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Glomerular filtration rate                 | 5                                                                       | 5          | 3           | 5          | 10                | 0                                                              | 0          |
|          | Glomerular filtration rate decreased       | 37                                                                      | 37         | 3           | 6          | 43                | 0                                                              | 0          |
|          | Glomerular filtration rate increased       | 2                                                                       | 2          | 1           | 2          | 4                 | 0                                                              | 0          |
|          | Glomerular filtration rate normal          | 17                                                                      | 17         | 1           | 1          | 18                | 0                                                              | 0          |
|          | Glucose urine                              | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Glucose urine absent                       | 4                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Glycosylated haemoglobin                   | 10                                                                      | 10         | 0           | 0          | 10                | 0                                                              | 0          |
|          | Glycosylated haemoglobin decreased         | 2                                                                       | 2          | 0           | 1          | 3                 | 0                                                              | 0          |
|          | Glycosylated haemoglobin increased         | 15                                                                      | 17         | 4           | 11         | 28                | 0                                                              | 0          |
|          | Glycosylated haemoglobin normal            | 3                                                                       | 3          | 1           | 3          | 6                 | 0                                                              | 0          |
|          | Gram stain                                 | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Gram stain negative                        | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Gram stain positive                        | 8                                                                       | 8          | 0           | 0          | 8                 | 0                                                              | 0          |
|          | Granulocyte count decreased                | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Granulocyte count increased                | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Granulocyte percentage                     | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Grip strength                              | 2                                                                       | 2          | 0           | 4          | 6                 | 0                                                              | 0          |
|          | Grip strength decreased                    | 34                                                                      | 57         | 27          | 80         | 137               | 0                                                              | 0          |
|          | Gynaecological examination                 | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Gynaecological examination abnormal        | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Gynaecological examination normal          | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | HIV test                                   | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | HIV test false positive                    | 0                                                                       | 0          | 0           | 3          | 3                 | 0                                                              | 0          |
|          | HIV test negative                          | 7                                                                       | 7          | 0           | 0          | 7                 | 0                                                              | 0          |
|          | HLA-B*27 assay                             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | HLA-B*27 positive                          | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Haematocrit                                | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Haematocrit decreased                      | 32                                                                      | 34         | 3           | 8          | 42                | 0                                                              | 0          |
|          | Haematocrit increased                      | 8                                                                       | 8          | 0           | 1          | 9                 | 0                                                              | 0          |
|          | Haematocrit normal                         | 21                                                                      | 21         | 1           | 2          | 23                | 0                                                              | 0          |
|          | Haematology test                           | 3                                                                       | 3          | 1           | 1          | 4                 | 0                                                              | 0          |
|          | Haemodynamic test                          | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Haemodynamic test normal                   | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Haemoglobin                                | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |

|          |                                          | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                          | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                       | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Haemoglobin E                            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Haemoglobin abnormal                     | 0                                                                       | 1          | 1           | 2          | 3                 | 0                                                              | 0          |
|          | Haemoglobin decreased                    | 88                                                                      | 108        | 11          | 19         | 127               | 0                                                              | 0          |
|          | Haemoglobin increased                    | 2                                                                       | 3          | 1           | 3          | 6                 | 0                                                              | 0          |
|          | Haemoglobin normal                       | 34                                                                      | 34         | 2           | 3          | 37                | 0                                                              | 0          |
|          | Haemophilus test positive                | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Haptoglobin decreased                    | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Haptoglobin normal                       | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Head lag                                 | 3                                                                       | 3          | 0           | 1          | 4                 | 0                                                              | 0          |
|          | Head lag abnormal                        | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Heart rate                               | 108                                                                     | 114        | 36          | 47         | 161               | 0                                                              | 0          |
|          | Heart rate abnormal                      | 27                                                                      | 32         | 39          | 93         | 125               | 0                                                              | 0          |
|          | Heart rate decreased                     | 34                                                                      | 61         | 41          | 148        | 209               | 0                                                              | 0          |
|          | Heart rate increased                     | 463                                                                     | 634        | 710         | 2683       | 3317              | 0                                                              | 0          |
|          | Heart rate irregular                     | 110                                                                     | 142        | 235         | 433        | 575               | 0                                                              | 0          |
|          | Heart rate normal                        | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Heart rate variability decreased         | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Heart rate variability increased         | 2                                                                       | 2          | 2           | 4          | 6                 | 0                                                              | 0          |
|          | Heart sounds                             | 2                                                                       | 2          | 2           | 2          | 4                 | 0                                                              | 0          |
|          | Heart sounds abnormal                    | 3                                                                       | 4          | 3           | 5          | 9                 | 0                                                              | 0          |
|          | Heavy metal normal                       | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Heavy metal test                         | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Heparin-induced thrombocytopenia test    | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Heparin-induced thrombocytopenia test po | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Hepatic enzyme                           | 3                                                                       | 3          | 0           | 1          | 4                 | 0                                                              | 0          |
|          | Hepatic enzyme abnormal                  | 3                                                                       | 4          | 3           | 9          | 13                | 0                                                              | 0          |
|          | Hepatic enzyme increased                 | 21                                                                      | 32         | 13          | 42         | 74                | 0                                                              | 0          |
|          | Hepatitis A antibody                     | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Hepatitis A antibody positive            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Hepatitis A virus test                   | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Hepatitis B core antibody                | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Hepatitis B core antibody positive       | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Hepatitis B surface antigen              | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Hepatitis C RNA                          | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Hepatitis C RNA positive                 | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Hepatitis C antibody negative            | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Hepatitis C antibody positive            | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Hepatitis C test negative                | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Hepatitis C virus test                   | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Hepatitis E antibody positive            | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Hepatitis viral test                     | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Hepatitis viral test negative            | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Hepatobiliary scan                       | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Hepatobiliary scan abnormal              | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Hepatobiliary scan normal                | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Herpes simplex test negative             | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Herpes simplex test positive             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | High density lipoprotein decreased       | 2                                                                       | 2          | 0           | 1          | 3                 | 0                                                              | 0          |
|          | High density lipoprotein increased       | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |

|          |                                            | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|--------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                            | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                         | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | High density lipoprotein normal            | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Histamine abnormal                         | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|          | Histamine level                            | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Histamine level increased                  | 2                                                                       | 2          | 0           | 1          | 3                 | 0                                                              | 0          |
|          | Hormone level abnormal                     | 17                                                                      | 17         | 30          | 38         | 55                | 0                                                              | 0          |
|          | Human chorionic gonadotropin               | 4                                                                       | 4          | 1           | 2          | 6                 | 0                                                              | 0          |
|          | Human chorionic gonadotropin decreased     | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Human chorionic gonadotropin increased     | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Human chorionic gonadotropin normal        | 0                                                                       | 0          | 2           | 2          | 2                 | 0                                                              | 0          |
|          | Human herpes virus 6 serology negative     | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Human herpes virus 6 serology positive     | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Human metapneumovirus test                 | 10                                                                      | 10         | 1           | 1          | 11                | 0                                                              | 0          |
|          | Human rhinovirus test                      | 11                                                                      | 11         | 1           | 1          | 12                | 0                                                              | 0          |
|          | Human rhinovirus test positive             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Hysteroscopy                               | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Imaging procedure                          | 7                                                                       | 7          | 1           | 1          | 8                 | 0                                                              | 0          |
|          | Imaging procedure abnormal                 | 6                                                                       | 7          | 0           | 1          | 8                 | 0                                                              | 0          |
|          | Immature granulocyte count                 | 16                                                                      | 16         | 0           | 0          | 16                | 0                                                              | 0          |
|          | Immature granulocyte count increased       | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Immature granulocyte percentage increase   | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Immunoglobulins decreased                  | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Immunoglobulins normal                     | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Immunology test                            | 4                                                                       | 4          | 2           | 3          | 7                 | 0                                                              | 0          |
|          | Immunology test abnormal                   | 0                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Immunology test normal                     | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Indeterminate investigation result         | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Inflammatory marker decreased              | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Inflammatory marker increased              | 22                                                                      | 26         | 6           | 9          | 35                | 0                                                              | 0          |
|          | Inflammatory marker test                   | 13                                                                      | 13         | 0           | 0          | 13                | 0                                                              | 0          |
|          | Influenza A virus test                     | 6                                                                       | 6          | 0           | 1          | 7                 | 0                                                              | 0          |
|          | Influenza A virus test negative            | 20                                                                      | 20         | 5           | 8          | 28                | 0                                                              | 0          |
|          | Influenza B virus test                     | 25                                                                      | 25         | 4           | 6          | 31                | 0                                                              | 0          |
|          | Influenza B virus test positive            | 0                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Influenza virus test                       | 6                                                                       | 6          | 1           | 5          | 11                | 0                                                              | 0          |
|          | Influenza virus test negative              | 22                                                                      | 22         | 8           | 15         | 37                | 0                                                              | 0          |
|          | Influenza virus test positive              | 0                                                                       | 2          | 0           | 1          | 3                 | 0                                                              | 0          |
|          | Inspiratory capacity decreased             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Interleukin level increased                | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | International normalised ratio             | 8                                                                       | 8          | 2           | 3          | 11                | 0                                                              | 0          |
|          | International normalised ratio abnormal    | 0                                                                       | 0          | 2           | 4          | 4                 | 0                                                              | 0          |
|          | International normalised ratio decreased   | 0                                                                       | 0          | 5           | 9          | 9                 | 0                                                              | 0          |
|          | International normalised ratio fluctuation | 0                                                                       | 0          | 0           | 3          | 3                 | 0                                                              | 0          |
|          | International normalised ratio increased   | 25                                                                      | 33         | 5           | 27         | 60                | 0                                                              | 0          |
|          | International normalised ratio normal      | 4                                                                       | 4          | 3           | 3          | 7                 | 0                                                              | 0          |
|          | Intestinal transit time abnormal           | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Intraocular pressure increased             | 4                                                                       | 6          | 1           | 5          | 11                | 0                                                              | 0          |
|          | Intraocular pressure test                  | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Investigation                              | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Investigation abnormal                     | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |

|          |                                               | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|-----------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                               | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                            | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Iron binding capacity total decreased         | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Iron binding capacity total normal            | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | JC polyomavirus test positive                 | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Joint position sense decreased                | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Klebsiella test positive                      | 7                                                                       | 7          | 0           | 0          | 7                 | 0                                                              | 0          |
|          | Laboratory test                               | 170                                                                     | 170        | 52          | 62         | 232               | 0                                                              | 0          |
|          | Laboratory test abnormal                      | 41                                                                      | 41         | 6           | 11         | 52                | 0                                                              | 0          |
|          | Laboratory test normal                        | 42                                                                      | 42         | 4           | 9          | 51                | 0                                                              | 0          |
|          | Laparoscopy                                   | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Laryngoscopy                                  | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Left ventricular end-diastolic pressure       | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Left ventricular end-diastolic pressure incre | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Legionella test                               | 14                                                                      | 14         | 0           | 0          | 14                | 0                                                              | 0          |
|          | Light chain analysis abnormal                 | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Light chain analysis increased                | 0                                                                       | 0          | 1           | 3          | 3                 | 0                                                              | 0          |
|          | Light chain analysis normal                   | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Limb girth decreased                          | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Lipase                                        | 3                                                                       | 3          | 1           | 2          | 5                 | 0                                                              | 0          |
|          | Lipase decreased                              | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Lipase increased                              | 6                                                                       | 12         | 4           | 7          | 19                | 0                                                              | 0          |
|          | Lipase normal                                 | 6                                                                       | 7          | 1           | 1          | 8                 | 0                                                              | 0          |
|          | Lipids                                        | 6                                                                       | 6          | 3           | 4          | 10                | 0                                                              | 0          |
|          | Lipids increased                              | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Lipids normal                                 | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Lipoprotein increased                         | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Liver function test                           | 5                                                                       | 5          | 3           | 3          | 8                 | 0                                                              | 0          |
|          | Liver function test abnormal                  | 8                                                                       | 11         | 6           | 12         | 23                | 0                                                              | 0          |
|          | Liver function test decreased                 | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Liver function test increased                 | 13                                                                      | 16         | 8           | 13         | 29                | 0                                                              | 0          |
|          | Liver function test normal                    | 4                                                                       | 4          | 1           | 3          | 7                 | 0                                                              | 0          |
|          | Liver iron concentration increased            | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Liver scan                                    | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Low density lipoprotein increased             | 4                                                                       | 4          | 2           | 4          | 8                 | 0                                                              | 0          |
|          | Low density lipoprotein normal                | 4                                                                       | 4          | 0           | 1          | 5                 | 0                                                              | 0          |
|          | Lumbar puncture                               | 27                                                                      | 32         | 0           | 1          | 33                | 0                                                              | 0          |
|          | Lumbar puncture abnormal                      | 12                                                                      | 13         | 0           | 1          | 14                | 0                                                              | 0          |
|          | Lumbar puncture normal                        | 5                                                                       | 5          | 0           | 1          | 6                 | 0                                                              | 0          |
|          | Lymph node palpable                           | 3                                                                       | 6          | 10          | 35         | 41                | 0                                                              | 0          |
|          | Lymph nodes scan abnormal                     | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Lymphocyte count                              | 13                                                                      | 13         | 1           | 1          | 14                | 0                                                              | 0          |
|          | Lymphocyte count abnormal                     | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Lymphocyte count decreased                    | 15                                                                      | 17         | 1           | 3          | 20                | 0                                                              | 0          |
|          | Lymphocyte count increased                    | 2                                                                       | 2          | 0           | 4          | 6                 | 0                                                              | 0          |
|          | Lymphocyte count normal                       | 4                                                                       | 4          | 2           | 2          | 6                 | 0                                                              | 0          |
|          | Lymphocyte morphology abnormal                | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Lymphocyte percentage                         | 9                                                                       | 9          | 1           | 1          | 10                | 0                                                              | 0          |
|          | Lymphocyte percentage decreased               | 29                                                                      | 29         | 1           | 1          | 30                | 0                                                              | 0          |
|          | Lymphocyte percentage increased               | 1                                                                       | 1          | 0           | 2          | 3                 | 0                                                              | 0          |
|          | Magnetic resonance imaging                    | 108                                                                     | 111        | 40          | 49         | 160               | 0                                                              | 0          |



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|          |                                            | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                         | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Magnetic resonance imaging abdominal       | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Magnetic resonance imaging abdominal ab    | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Magnetic resonance imaging abdominal no    | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Magnetic resonance imaging abnormal        | 24                                                                      | 27         | 9           | 14         | 41                | 0                                                              | 0          |
|          | Magnetic resonance imaging head            | 39                                                                      | 39         | 13          | 13         | 52                | 0                                                              | 0          |
|          | Magnetic resonance imaging head abnormal   | 55                                                                      | 55         | 5           | 5          | 60                | 0                                                              | 0          |
|          | Magnetic resonance imaging head normal     | 25                                                                      | 25         | 1           | 1          | 26                | 0                                                              | 0          |
|          | Magnetic resonance imaging heart           | 15                                                                      | 15         | 6           | 6          | 21                | 0                                                              | 0          |
|          | Magnetic resonance imaging hepatobiliary   | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Magnetic resonance imaging joint           | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Magnetic resonance imaging neck            | 9                                                                       | 9          | 2           | 2          | 11                | 0                                                              | 0          |
|          | Magnetic resonance imaging normal          | 25                                                                      | 25         | 8           | 8          | 33                | 0                                                              | 0          |
|          | Magnetic resonance imaging spinal          | 9                                                                       | 9          | 0           | 0          | 9                 | 0                                                              | 0          |
|          | Magnetic resonance imaging spinal abnormal | 13                                                                      | 13         | 1           | 1          | 14                | 0                                                              | 0          |
|          | Magnetic resonance imaging spinal normal   | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Magnetic resonance imaging thoracic        | 3                                                                       | 3          | 1           | 1          | 4                 | 0                                                              | 0          |
|          | Magnetic resonance imaging thoracic abno   | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Magnetic resonance imaging thoracic norm   | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Mammogram                                  | 3                                                                       | 3          | 0           | 1          | 4                 | 0                                                              | 0          |
|          | Mammogram abnormal                         | 2                                                                       | 2          | 1           | 3          | 5                 | 0                                                              | 0          |
|          | Mammogram normal                           | 1                                                                       | 1          | 1           | 3          | 4                 | 0                                                              | 0          |
|          | Maximum heart rate increased               | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Mean cell haemoglobin                      | 2                                                                       | 2          | 0           | 1          | 3                 | 0                                                              | 0          |
|          | Mean cell haemoglobin concentration        | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Mean cell haemoglobin concentration decr   | 8                                                                       | 8          | 1           | 1          | 9                 | 0                                                              | 0          |
|          | Mean cell haemoglobin concentration incre  | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Mean cell haemoglobin concentration norm   | 29                                                                      | 29         | 1           | 1          | 30                | 0                                                              | 0          |
|          | Mean cell haemoglobin decreased            | 2                                                                       | 2          | 1           | 1          | 3                 | 0                                                              | 0          |
|          | Mean cell haemoglobin increased            | 15                                                                      | 15         | 0           | 1          | 16                | 0                                                              | 0          |
|          | Mean cell haemoglobin normal               | 21                                                                      | 21         | 2           | 2          | 23                | 0                                                              | 0          |
|          | Mean cell volume                           | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Mean cell volume decreased                 | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Mean cell volume increased                 | 15                                                                      | 15         | 0           | 0          | 15                | 0                                                              | 0          |
|          | Mean cell volume normal                    | 33                                                                      | 33         | 3           | 3          | 36                | 0                                                              | 0          |
|          | Mean platelet volume                       | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Mean platelet volume decreased             | 4                                                                       | 4          | 1           | 1          | 5                 | 0                                                              | 0          |
|          | Mean platelet volume increased             | 10                                                                      | 10         | 1           | 1          | 11                | 0                                                              | 0          |
|          | Mean platelet volume normal                | 16                                                                      | 16         | 1           | 1          | 17                | 0                                                              | 0          |
|          | Mediastinoscopy                            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Medical observation                        | 0                                                                       | 0          | 0           | 6          | 6                 | 0                                                              | 0          |
|          | Megakaryocytes normal                      | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Menstruation normal                        | 0                                                                       | 0          | 6           | 11         | 11                | 0                                                              | 0          |
|          | Metabolic function test                    | 88                                                                      | 89         | 40          | 54         | 143               | 0                                                              | 0          |
|          | Metabolic function test abnormal           | 16                                                                      | 18         | 1           | 1          | 19                | 0                                                              | 0          |
|          | Metabolic function test normal             | 16                                                                      | 16         | 5           | 6          | 22                | 0                                                              | 0          |
|          | Metamyelocyte percentage                   | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Microscopy                                 | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Model for end stage liver disease score    | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Monoclonal immunoglobulin increased        | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |

|          |                                            | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|--------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                            | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                         | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Monoclonal immunoglobulin present          | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Monocyte count                             | 19                                                                      | 19         | 0           | 0          | 19                | 0                                                              | 0          |
|          | Monocyte count decreased                   | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Monocyte count increased                   | 6                                                                       | 6          | 4           | 5          | 11                | 0                                                              | 0          |
|          | Monocyte count normal                      | 9                                                                       | 9          | 1           | 1          | 10                | 0                                                              | 0          |
|          | Monocyte percentage                        | 20                                                                      | 20         | 2           | 2          | 22                | 0                                                              | 0          |
|          | Monocyte percentage decreased              | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Monocyte percentage increased              | 14                                                                      | 14         | 0           | 0          | 14                | 0                                                              | 0          |
|          | Mononucleosis heterophile test             | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Montreal cognitive assessment              | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Moraxella test positive                    | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Multipathogen PCR test                     | 2                                                                       | 2          | 1           | 1          | 3                 | 0                                                              | 0          |
|          | Mumps antibody test                        | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Murphy's sign test                         | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Muscle strength abnormal                   | 2                                                                       | 4          | 6           | 14         | 18                | 0                                                              | 0          |
|          | Mycobacterium tuberculosis complex test    | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Mycobacterium tuberculosis complex test p  | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Mycoplasma test negative                   | 9                                                                       | 9          | 1           | 1          | 10                | 0                                                              | 0          |
|          | Mycoplasma test positive                   | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Myocardial necrosis marker                 | 4                                                                       | 5          | 0           | 2          | 7                 | 0                                                              | 0          |
|          | Myocardial necrosis marker increased       | 13                                                                      | 20         | 0           | 0          | 20                | 0                                                              | 0          |
|          | Myocardial necrosis marker normal          | 3                                                                       | 3          | 0           | 2          | 5                 | 0                                                              | 0          |
|          | Myocardial strain imaging                  | 3                                                                       | 22         | 0           | 3          | 25                | 0                                                              | 0          |
|          | Myocardial strain imaging abnormal         | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Myoglobin blood                            | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | N-telopeptide                              | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | N-terminal prohormone brain natriuretic pe | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | N-terminal prohormone brain natriuretic pe | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | N-terminal prohormone brain natriuretic pe | 11                                                                      | 11         | 2           | 4          | 15                | 0                                                              | 0          |
|          | NIH stroke scale                           | 2                                                                       | 2          | 0           | 2          | 4                 | 0                                                              | 0          |
|          | NIH stroke scale score increased           | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Nerve conduction studies                   | 9                                                                       | 9          | 2           | 2          | 11                | 0                                                              | 0          |
|          | Nerve conduction studies abnormal          | 5                                                                       | 5          | 0           | 1          | 6                 | 0                                                              | 0          |
|          | Nerve conduction studies normal            | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Nerve stimulation test                     | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Nerve stimulation test abnormal            | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Nerve stimulation test normal              | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Neurological examination                   | 9                                                                       | 9          | 1           | 3          | 12                | 0                                                              | 0          |
|          | Neurological examination abnormal          | 3                                                                       | 3          | 3           | 3          | 6                 | 0                                                              | 0          |
|          | Neurological examination normal            | 3                                                                       | 3          | 1           | 1          | 4                 | 0                                                              | 0          |
|          | Neutralising antibodies negative           | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Neutrophil count                           | 20                                                                      | 20         | 2           | 2          | 22                | 0                                                              | 0          |
|          | Neutrophil count abnormal                  | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Neutrophil count decreased                 | 5                                                                       | 6          | 3           | 6          | 12                | 0                                                              | 0          |
|          | Neutrophil count increased                 | 9                                                                       | 9          | 3           | 5          | 14                | 0                                                              | 0          |
|          | Neutrophil count normal                    | 8                                                                       | 8          | 1           | 1          | 9                 | 0                                                              | 0          |
|          | Neutrophil percentage                      | 6                                                                       | 6          | 2           | 2          | 8                 | 0                                                              | 0          |
|          | Neutrophil percentage decreased            | 4                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Neutrophil percentage increased            | 27                                                                      | 28         | 0           | 1          | 29                | 0                                                              | 0          |

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|----------|-------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                           | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                        | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Neutrophil toxic granulation present      | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Nitrite urine                             | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Nitrite urine absent                      | 8                                                                       | 8          | 0           | 0          | 8                 | 0                                                              | 0          |
|          | Nitrite urine present                     | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Non-high-density lipoprotein cholesterol  | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Norepinephrine increased                  | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Norovirus test                            | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Nucleic acid test                         | 8                                                                       | 8          | 3           | 3          | 11                | 0                                                              | 0          |
|          | Nutritional condition abnormal            | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Occult blood                              | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Occult blood negative                     | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Occult blood positive                     | 3                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Oesophagogastroduodenoscopy               | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Oesophagogastroduodenoscopy abnormal      | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Oesophagogastroduodenoscopy normal        | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Ophthalmic scan                           | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Ophthalmological examination              | 5                                                                       | 6          | 1           | 5          | 11                | 0                                                              | 0          |
|          | Ophthalmological examination abnormal     | 6                                                                       | 6          | 0           | 0          | 6                 | 0                                                              | 0          |
|          | Ophthalmological examination normal       | 1                                                                       | 2          | 1           | 1          | 3                 | 0                                                              | 0          |
|          | Opiates positive                          | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Optical coherence tomography              | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Oral soft tissue biopsy                   | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Orthostatic heart rate response increased | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Oxygen consumption                        | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Oxygen consumption decreased              | 0                                                                       | 0          | 3           | 6          | 6                 | 0                                                              | 0          |
|          | Oxygen consumption increased              | 2                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Oxygen saturation                         | 3                                                                       | 3          | 1           | 11         | 14                | 0                                                              | 0          |
|          | Oxygen saturation abnormal                | 4                                                                       | 7          | 3           | 14         | 21                | 0                                                              | 0          |
|          | Oxygen saturation decreased               | 140                                                                     | 233        | 42          | 141        | 374               | 0                                                              | 0          |
|          | Oxygen saturation increased               | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|          | PCO2 decreased                            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | PCO2 increased                            | 8                                                                       | 9          | 0           | 0          | 9                 | 0                                                              | 0          |
|          | PCO2 normal                               | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | PO2 decreased                             | 9                                                                       | 11         | 0           | 0          | 11                | 0                                                              | 0          |
|          | PO2 increased                             | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Pain assessment                           | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|          | Palpatory finding abnormal                | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Pancreatic enzymes increased              | 0                                                                       | 1          | 0           | 3          | 4                 | 0                                                              | 0          |
|          | Panel-reactive antibody                   | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Paracentesis eye                          | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Parvovirus B19 test                       | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Pathology test                            | 6                                                                       | 6          | 0           | 0          | 6                 | 0                                                              | 0          |
|          | Peak expiratory flow rate                 | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Perfusion brain scan normal               | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Pericardial drainage test abnormal        | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Philadelphia chromosome positive          | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Physical examination                      | 0                                                                       | 0          | 2           | 7          | 7                 | 0                                                              | 0          |
|          | Platelet aggregation abnormal             | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Platelet count                            | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |

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|----------|--------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                            | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                         | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Platelet count abnormal                    | 1                                                                       | 2          | 1           | 2          | 4                 | 0                                                              | 0          |
|          | Platelet count decreased                   | 69                                                                      | 116        | 44          | 89         | 205               | 0                                                              | 0          |
|          | Platelet count increased                   | 17                                                                      | 18         | 9           | 18         | 36                | 0                                                              | 0          |
|          | Platelet count normal                      | 43                                                                      | 43         | 6           | 6          | 49                | 0                                                              | 0          |
|          | Platelet morphology abnormal               | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Platelet morphology normal                 | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Pleural fluid analysis abnormal            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Polymerase chain reaction                  | 11                                                                      | 11         | 0           | 4          | 15                | 0                                                              | 0          |
|          | Polymerase chain reaction positive         | 1                                                                       | 1          | 3           | 3          | 4                 | 0                                                              | 0          |
|          | Popliteal pulse decreased                  | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Portogram                                  | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Positron emission tomogram                 | 5                                                                       | 5          | 1           | 1          | 6                 | 0                                                              | 0          |
|          | Positron emission tomogram abnormal        | 2                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Positron emission tomogram normal          | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Prealbumin decreased                       | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Precancerous cells present                 | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Pregnancy test                             | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Pregnancy test negative                    | 1                                                                       | 2          | 0           | 3          | 5                 | 0                                                              | 0          |
|          | Pregnancy test positive                    | 0                                                                       | 0          | 2           | 2          | 2                 | 0                                                              | 0          |
|          | Pregnancy test urine negative              | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Prenatal screening test                    | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Prenatal screening test abnormal           | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Procalcitonin                              | 34                                                                      | 34         | 1           | 2          | 36                | 0                                                              | 0          |
|          | Procalcitonin decreased                    | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Procalcitonin increased                    | 19                                                                      | 22         | 0           | 0          | 22                | 0                                                              | 0          |
|          | Procalcitonin normal                       | 6                                                                       | 6          | 0           | 0          | 6                 | 0                                                              | 0          |
|          | Proctoscopy                                | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Product residue present                    | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Progesterone                               | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Prohormone brain natriuretic peptide incre | 7                                                                       | 7          | 0           | 0          | 7                 | 0                                                              | 0          |
|          | Prostatic specific antigen                 | 4                                                                       | 4          | 0           | 1          | 5                 | 0                                                              | 0          |
|          | Prostatic specific antigen decreased       | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|          | Prostatic specific antigen increased       | 1                                                                       | 2          | 5           | 11         | 13                | 0                                                              | 0          |
|          | Prostatic specific antigen normal          | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Protein C                                  | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Protein C increased                        | 2                                                                       | 3          | 2           | 2          | 5                 | 0                                                              | 0          |
|          | Protein S                                  | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Protein S normal                           | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Protein total                              | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Protein total abnormal                     | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Protein total decreased                    | 11                                                                      | 11         | 0           | 1          | 12                | 0                                                              | 0          |
|          | Protein total increased                    | 3                                                                       | 3          | 1           | 2          | 5                 | 0                                                              | 0          |
|          | Protein total normal                       | 21                                                                      | 21         | 2           | 2          | 23                | 0                                                              | 0          |
|          | Protein urine                              | 3                                                                       | 3          | 1           | 1          | 4                 | 0                                                              | 0          |
|          | Protein urine absent                       | 4                                                                       | 4          | 0           | 1          | 5                 | 0                                                              | 0          |
|          | Protein urine present                      | 4                                                                       | 4          | 1           | 1          | 5                 | 0                                                              | 0          |
|          | Prothrombin consumption time prolonged     | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Prothrombin level                          | 2                                                                       | 2          | 1           | 1          | 3                 | 0                                                              | 0          |
|          | Prothrombin level decreased                | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |

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|          |                                             | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                          | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Prothrombin level increased                 | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Prothrombin level normal                    | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Prothrombin time                            | 10                                                                      | 10         | 0           | 1          | 11                | 0                                                              | 0          |
|          | Prothrombin time abnormal                   | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Prothrombin time normal                     | 2                                                                       | 2          | 1           | 1          | 3                 | 0                                                              | 0          |
|          | Prothrombin time prolonged                  | 11                                                                      | 13         | 3           | 5          | 18                | 0                                                              | 0          |
|          | Prothrombin time shortened                  | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Pseudomonas test positive                   | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Psychiatric evaluation                      | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Pulmonary arterial pressure increased       | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Pulmonary arterial wedge pressure decreased | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Pulmonary function test                     | 5                                                                       | 5          | 1           | 3          | 8                 | 0                                                              | 0          |
|          | Pulmonary function test decreased           | 3                                                                       | 4          | 0           | 4          | 8                 | 0                                                              | 0          |
|          | Pulmonary function test normal              | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Pulmonary imaging procedure                 | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Pulmonary imaging procedure abnormal        | 3                                                                       | 3          | 1           | 1          | 4                 | 0                                                              | 0          |
|          | Pulmonary physical examination              | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Pulse abnormal                              | 6                                                                       | 9          | 14          | 44         | 53                | 0                                                              | 0          |
|          | Pulse absent                                | 17                                                                      | 49         | 1           | 10         | 59                | 0                                                              | 0          |
|          | Pulse pressure increased                    | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Pulse volume decreased                      | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Pulse waveform normal                       | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Pupil dilation procedure                    | 4                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Pupillary light reflex tests abnormal       | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Pus in stool                                | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | QRS axis                                    | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | QRS axis abnormal                           | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Quality of life decreased                   | 6                                                                       | 7          | 10          | 17         | 24                | 0                                                              | 0          |
|          | Radial pulse                                | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Red blood cell count                        | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Red blood cell count abnormal               | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Red blood cell count decreased              | 36                                                                      | 39         | 4           | 7          | 46                | 0                                                              | 0          |
|          | Red blood cell count increased              | 4                                                                       | 4          | 1           | 2          | 6                 | 0                                                              | 0          |
|          | Red blood cell count normal                 | 13                                                                      | 14         | 2           | 2          | 16                | 0                                                              | 0          |
|          | Red blood cell microcytes present           | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Red blood cell morphology abnormal          | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Red blood cell morphology normal            | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Red blood cell nucleated morphology         | 13                                                                      | 13         | 0           | 0          | 13                | 0                                                              | 0          |
|          | Red blood cell nucleated morphology present | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Red blood cell scan                         | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Red blood cell schistocytes present         | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Red blood cell sedimentation rate           | 7                                                                       | 7          | 4           | 6          | 13                | 0                                                              | 0          |
|          | Red blood cell sedimentation rate increased | 18                                                                      | 21         | 12          | 20         | 41                | 0                                                              | 0          |
|          | Red blood cell sedimentation rate normal    | 7                                                                       | 7          | 7           | 8          | 15                | 0                                                              | 0          |
|          | Red blood cells urine                       | 1                                                                       | 1          | 1           | 2          | 3                 | 0                                                              | 0          |
|          | Red blood cells urine positive              | 6                                                                       | 6          | 0           | 1          | 7                 | 0                                                              | 0          |
|          | Red cell distribution width                 | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Red cell distribution width decreased       | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Red cell distribution width increased       | 12                                                                      | 12         | 0           | 0          | 12                | 0                                                              | 0          |

|          |                                               | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|-----------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                               | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                            | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Red cell distribution width normal            | 26                                                                      | 26         | 3           | 3          | 29                | 0                                                              | 0          |
|          | Reflex test normal                            | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Renal function test                           | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Renal function test abnormal                  | 3                                                                       | 4          | 1           | 2          | 6                 | 0                                                              | 0          |
|          | Renal function test normal                    | 5                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Renin decreased                               | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Respiratory rate                              | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Respiratory rate decreased                    | 7                                                                       | 7          | 3           | 10         | 17                | 0                                                              | 0          |
|          | Respiratory rate increased                    | 12                                                                      | 25         | 15          | 71         | 96                | 0                                                              | 0          |
|          | Respiratory syncytial virus test              | 5                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Respiratory syncytial virus test negative     | 20                                                                      | 20         | 2           | 2          | 22                | 0                                                              | 0          |
|          | Respiratory syncytial virus test positive     | 2                                                                       | 2          | 1           | 1          | 3                 | 0                                                              | 0          |
|          | Respiratory viral panel                       | 14                                                                      | 14         | 2           | 4          | 18                | 0                                                              | 0          |
|          | Reticulocyte count increased                  | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Retinogram abnormal                           | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Rhesus antibodies positive                    | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Rheumatoid factor                             | 1                                                                       | 1          | 3           | 4          | 5                 | 0                                                              | 0          |
|          | Rheumatoid factor increased                   | 3                                                                       | 3          | 2           | 2          | 5                 | 0                                                              | 0          |
|          | Rheumatoid factor negative                    | 3                                                                       | 3          | 3           | 5          | 8                 | 0                                                              | 0          |
|          | Rheumatoid factor positive                    | 1                                                                       | 1          | 1           | 2          | 3                 | 0                                                              | 0          |
|          | Rheumatological examination                   | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Right ventricular ejection fraction decrease  | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Right ventricular systolic pressure           | 6                                                                       | 6          | 0           | 0          | 6                 | 0                                                              | 0          |
|          | Right ventricular systolic pressure decrease  | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Right ventricular systolic pressure increased | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Romberg test                                  | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Romberg test positive                         | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Rotavirus test negative                       | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Russell's viper venom time normal             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | SARS-CoV-1 test negative                      | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | SARS-CoV-1 test positive                      | 1                                                                       | 1          | 1           | 4          | 5                 | 0                                                              | 0          |
|          | SARS-CoV-2 RNA                                | 12                                                                      | 12         | 7           | 8          | 20                | 0                                                              | 0          |
|          | SARS-CoV-2 RNA increased                      | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | SARS-CoV-2 antibody test                      | 4                                                                       | 4          | 3           | 14         | 18                | 0                                                              | 0          |
|          | SARS-CoV-2 antibody test negative             | 4                                                                       | 4          | 5           | 39         | 43                | 0                                                              | 0          |
|          | SARS-CoV-2 antibody test positive             | 5                                                                       | 7          | 7           | 29         | 36                | 0                                                              | 0          |
|          | SARS-CoV-2 test                               | 39                                                                      | 39         | 17          | 47         | 86                | 0                                                              | 0          |
|          | SARS-CoV-2 test false negative                | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | SARS-CoV-2 test false positive                | 0                                                                       | 1          | 1           | 5          | 6                 | 0                                                              | 0          |
|          | SARS-CoV-2 test negative                      | 67                                                                      | 69         | 42          | 120        | 189               | 0                                                              | 0          |
|          | SARS-CoV-2 test positive                      | 1104                                                                    | 1157       | 998         | 1549       | 2706              | 0                                                              | 0          |
|          | Saliva analysis                               | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Salmonella test negative                      | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Scan                                          | 6                                                                       | 6          | 4           | 4          | 10                | 0                                                              | 0          |
|          | Scan abdomen abnormal                         | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Scan abnormal                                 | 2                                                                       | 2          | 1           | 1          | 3                 | 0                                                              | 0          |
|          | Scan brain                                    | 4                                                                       | 4          | 1           | 1          | 5                 | 0                                                              | 0          |
|          | Scan myocardial perfusion                     | 4                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Scan normal                                   | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |

|          |                                   | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|-----------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                   | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Scan with contrast                | 31                                                                      | 31         | 5           | 5          | 36                | 0                                                              | 0          |
|          | Scan with contrast abnormal       | 37                                                                      | 37         | 4           | 4          | 41                | 0                                                              | 0          |
|          | Scan with contrast normal         | 10                                                                      | 10         | 2           | 2          | 12                | 0                                                              | 0          |
|          | Semen analysis abnormal           | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Semen volume decreased            | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Sensory level                     | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Sensory level abnormal            | 1                                                                       | 2          | 17          | 18         | 20                | 0                                                              | 0          |
|          | Seroconversion test negative      | 0                                                                       | 0          | 2           | 3          | 3                 | 0                                                              | 0          |
|          | Serology normal                   | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Serratia test positive            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Serum ferritin                    | 6                                                                       | 6          | 1           | 1          | 7                 | 0                                                              | 0          |
|          | Serum ferritin decreased          | 3                                                                       | 3          | 3           | 4          | 7                 | 0                                                              | 0          |
|          | Serum ferritin increased          | 16                                                                      | 16         | 1           | 3          | 19                | 0                                                              | 0          |
|          | Serum ferritin normal             | 4                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Sexually transmitted disease test | 0                                                                       | 0          | 2           | 2          | 2                 | 0                                                              | 0          |
|          | Shift to the left                 | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Sinus rhythm                      | 5                                                                       | 7          | 5           | 12         | 19                | 0                                                              | 0          |
|          | Skin temperature                  | 10                                                                      | 10         | 7           | 9          | 19                | 0                                                              | 0          |
|          | Skin test                         | 1                                                                       | 1          | 0           | 2          | 3                 | 0                                                              | 0          |
|          | Skin test negative                | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Skin test positive                | 0                                                                       | 1          | 1           | 3          | 4                 | 0                                                              | 0          |
|          | Skin turgor decreased             | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Skull X-ray                       | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Sleep study                       | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Smear cervix                      | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Smear cervix abnormal             | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Smear test                        | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Smear vaginal normal              | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Smooth muscle antibody            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Smooth muscle antibody positive   | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Specific gravity body fluid       | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Specific gravity urine decreased  | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Specific gravity urine normal     | 5                                                                       | 5          | 0           | 1          | 6                 | 0                                                              | 0          |
|          | Spinal X-ray abnormal             | 2                                                                       | 3          | 1           | 1          | 4                 | 0                                                              | 0          |
|          | Spinal X-ray normal               | 2                                                                       | 2          | 0           | 1          | 3                 | 0                                                              | 0          |
|          | Spirometry                        | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Sputum abnormal                   | 0                                                                       | 1          | 1           | 4          | 5                 | 0                                                              | 0          |
|          | Sputum culture                    | 8                                                                       | 8          | 0           | 0          | 8                 | 0                                                              | 0          |
|          | Sputum culture positive           | 5                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Staphylococcus test               | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Staphylococcus test negative      | 7                                                                       | 7          | 0           | 0          | 7                 | 0                                                              | 0          |
|          | Staphylococcus test positive      | 13                                                                      | 13         | 0           | 0          | 13                | 0                                                              | 0          |
|          | Steroid activity                  | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Stool analysis                    | 1                                                                       | 1          | 0           | 2          | 3                 | 0                                                              | 0          |
|          | Stool analysis abnormal           | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Stool analysis normal             | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Streptococcus test                | 3                                                                       | 3          | 2           | 3          | 6                 | 0                                                              | 0          |
|          | Streptococcus test negative       | 11                                                                      | 11         | 3           | 4          | 15                | 0                                                              | 0          |
|          | Streptococcus test positive       | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |

|          |                                            | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|--------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                            | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                         | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Stress echocardiogram                      | 2                                                                       | 2          | 7           | 7          | 9                 | 0                                                              | 0          |
|          | Stress echocardiogram abnormal             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Stroke volume                              | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Stroke volume decreased                    | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Swallow study                              | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Swollen joint count                        | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|          | Synovial fluid analysis abnormal           | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Synovial fluid crystal present             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Systemic lupus erythematosus disease activ | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | T-lymphocyte count abnormal                | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Temperature difference of extremities      | 3                                                                       | 4          | 4           | 6          | 10                | 0                                                              | 0          |
|          | Temperature perception test abnormal       | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Temperature perception test decreased      | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Tender joint count                         | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Thrombin time prolonged                    | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Thromboelastogram                          | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Thyroglobulin increased                    | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Thyroid function test                      | 8                                                                       | 8          | 0           | 0          | 8                 | 0                                                              | 0          |
|          | Thyroid function test abnormal             | 1                                                                       | 1          | 4           | 4          | 5                 | 0                                                              | 0          |
|          | Thyroid function test normal               | 6                                                                       | 6          | 1           | 2          | 8                 | 0                                                              | 0          |
|          | Thyroid gland scan abnormal                | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Thyroid hormones decreased                 | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Thyroid hormones increased                 | 0                                                                       | 0          | 1           | 3          | 3                 | 0                                                              | 0          |
|          | Thyroid hormones test                      | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Thyroid stimulating immunoglobulin increa  | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Thyroxine                                  | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Thyroxine decreased                        | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Thyroxine free                             | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Thyroxine free decreased                   | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Thyroxine free increased                   | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Thyroxine free normal                      | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Thyroxine increased                        | 1                                                                       | 1          | 0           | 2          | 3                 | 0                                                              | 0          |
|          | Tilt table test                            | 2                                                                       | 2          | 1           | 1          | 3                 | 0                                                              | 0          |
|          | Tilt table test positive                   | 0                                                                       | 0          | 2           | 2          | 2                 | 0                                                              | 0          |
|          | Topography corneal abnormal                | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Total bile acids increased                 | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Total fluid output                         | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Total lung capacity decreased              | 5                                                                       | 6          | 3           | 4          | 10                | 0                                                              | 0          |
|          | Toxicologic test                           | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Toxicologic test normal                    | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Toxoplasma serology negative               | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Transaminases                              | 0                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Transaminases abnormal                     | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Transaminases increased                    | 23                                                                      | 27         | 7           | 10         | 37                | 0                                                              | 0          |
|          | Transferrin decreased                      | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Transferrin saturation decreased           | 2                                                                       | 2          | 0           | 1          | 3                 | 0                                                              | 0          |
|          | Transvalvular pressure gradient            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Treponema test                             | 2                                                                       | 2          | 1           | 1          | 3                 | 0                                                              | 0          |
|          | Treponema test positive                    | 0                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |



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|          |                                      | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                   | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Tri-iodothyronine                    | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Tri-iodothyronine abnormal           | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Tri-iodothyronine decreased          | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Tri-iodothyronine free increased     | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Tri-iodothyronine increased          | 2                                                                       | 2          | 0           | 2          | 4                 | 0                                                              | 0          |
|          | Troponin                             | 39                                                                      | 39         | 17          | 24         | 63                | 0                                                              | 0          |
|          | Troponin I                           | 6                                                                       | 7          | 4           | 4          | 11                | 0                                                              | 0          |
|          | Troponin I abnormal                  | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Troponin I increased                 | 25                                                                      | 25         | 2           | 2          | 27                | 0                                                              | 0          |
|          | Troponin I normal                    | 8                                                                       | 8          | 0           | 0          | 8                 | 0                                                              | 0          |
|          | Troponin T                           | 2                                                                       | 2          | 1           | 1          | 3                 | 0                                                              | 0          |
|          | Troponin T increased                 | 9                                                                       | 9          | 1           | 1          | 10                | 0                                                              | 0          |
|          | Troponin T normal                    | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Troponin decreased                   | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Troponin increased                   | 135                                                                     | 169        | 9           | 19         | 188               | 0                                                              | 0          |
|          | Troponin normal                      | 26                                                                      | 27         | 13          | 15         | 42                | 0                                                              | 0          |
|          | Tryptase                             | 1                                                                       | 1          | 0           | 4          | 5                 | 0                                                              | 0          |
|          | Tuberculin test                      | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Tumour marker increased              | 3                                                                       | 3          | 2           | 4          | 7                 | 0                                                              | 0          |
|          | Tympanometry                         | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Ultrasound Doppler                   | 30                                                                      | 30         | 8           | 11         | 41                | 0                                                              | 0          |
|          | Ultrasound Doppler abnormal          | 40                                                                      | 44         | 12          | 13         | 57                | 0                                                              | 0          |
|          | Ultrasound Doppler normal            | 23                                                                      | 24         | 2           | 2          | 26                | 0                                                              | 0          |
|          | Ultrasound abdomen                   | 6                                                                       | 6          | 0           | 2          | 8                 | 0                                                              | 0          |
|          | Ultrasound abdomen abnormal          | 9                                                                       | 10         | 1           | 2          | 12                | 0                                                              | 0          |
|          | Ultrasound abdomen normal            | 3                                                                       | 3          | 0           | 1          | 4                 | 0                                                              | 0          |
|          | Ultrasound antenatal screen          | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Ultrasound antenatal screen abnormal | 6                                                                       | 7          | 0           | 0          | 7                 | 0                                                              | 0          |
|          | Ultrasound antenatal screen normal   | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Ultrasound biliary tract             | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Ultrasound bladder                   | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Ultrasound bladder abnormal          | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Ultrasound bladder normal            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Ultrasound breast                    | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|          | Ultrasound breast abnormal           | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Ultrasound chest                     | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Ultrasound foetal                    | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Ultrasound foetal abnormal           | 3                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Ultrasound head                      | 2                                                                       | 2          | 0           | 1          | 3                 | 0                                                              | 0          |
|          | Ultrasound head normal               | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Ultrasound kidney                    | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Ultrasound kidney abnormal           | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Ultrasound kidney normal             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Ultrasound liver                     | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Ultrasound liver normal              | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Ultrasound ovary abnormal            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Ultrasound pelvis abnormal           | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Ultrasound pelvis normal             | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Ultrasound scan                      | 36                                                                      | 36         | 30          | 38         | 74                | 0                                                              | 0          |

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|----------|------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                          | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                       | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Ultrasound scan abnormal                 | 12                                                                      | 12         | 25          | 29         | 41                | 0                                                              | 0          |
|          | Ultrasound scan normal                   | 11                                                                      | 11         | 7           | 8          | 19                | 0                                                              | 0          |
|          | Ultrasound scan vagina                   | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Ultrasound scan vagina abnormal          | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Ultrasound scan vagina normal            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Ultrasound testes                        | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Ultrasound testes normal                 | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Ultrasound thyroid abnormal              | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Ultrasound uterus abnormal               | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Ureteroscopy                             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Urinary casts                            | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Urinary casts present                    | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Urinary sediment present                 | 5                                                                       | 6          | 1           | 1          | 7                 | 0                                                              | 0          |
|          | Urinary system X-ray                     | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Urine albumin/creatinine ratio           | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Urine analysis                           | 42                                                                      | 42         | 11          | 25         | 67                | 0                                                              | 0          |
|          | Urine analysis abnormal                  | 20                                                                      | 20         | 4           | 14         | 34                | 0                                                              | 0          |
|          | Urine analysis normal                    | 27                                                                      | 27         | 2           | 5          | 32                | 0                                                              | 0          |
|          | Urine bilirubin decreased                | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Urine ketone body                        | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Urine ketone body absent                 | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Urine ketone body present                | 5                                                                       | 6          | 0           | 3          | 9                 | 0                                                              | 0          |
|          | Urine leukocyte esterase                 | 7                                                                       | 7          | 1           | 3          | 10                | 0                                                              | 0          |
|          | Urine leukocyte esterase positive        | 5                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Urine osmolality                         | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Urine osmolality increased               | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Urine output                             | 3                                                                       | 3          | 2           | 4          | 7                 | 0                                                              | 0          |
|          | Urine output decreased                   | 12                                                                      | 16         | 1           | 14         | 30                | 0                                                              | 0          |
|          | Urine output increased                   | 0                                                                       | 0          | 5           | 13         | 13                | 0                                                              | 0          |
|          | Urine protein/creatinine ratio           | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Urine sodium                             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Urobilinogen urine                       | 6                                                                       | 6          | 0           | 2          | 8                 | 0                                                              | 0          |
|          | Urobilinogen urine increased             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Urogram                                  | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Urogram abnormal                         | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Urogram normal                           | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Varicella virus test                     | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Varicella virus test negative            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Varicella virus test positive            | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Vascular imaging                         | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Vascular resistance systemic             | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Vascular test                            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Venogram                                 | 4                                                                       | 4          | 1           | 1          | 5                 | 0                                                              | 0          |
|          | Venogram abnormal                        | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Venogram normal                          | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Venous oxygen partial pressure decreased | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Venous oxygen saturation decreased       | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Venous pressure jugular                  | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Ventilation/perfusion scan               | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |

|          |                                     | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|-------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                     | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                  | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Ventilation/perfusion scan abnormal | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Very low density lipoprotein        | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Vestibular function test abnormal   | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Vestibular function test normal     | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Viral load increased                | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Viral test                          | 2                                                                       | 2          | 0           | 1          | 3                 | 0                                                              | 0          |
|          | Viral test negative                 | 6                                                                       | 6          | 0           | 0          | 6                 | 0                                                              | 0          |
|          | Viral test positive                 | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Viral titre decreased               | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|          | Viral titre increased               | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Visual field tests                  | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Visual field tests abnormal         | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Visual tracking test                | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Vital functions abnormal            | 1                                                                       | 2          | 0           | 3          | 5                 | 0                                                              | 0          |
|          | Vital signs measurement             | 0                                                                       | 0          | 1           | 30         | 30                | 0                                                              | 0          |
|          | Vitamin B12                         | 4                                                                       | 4          | 3           | 3          | 7                 | 0                                                              | 0          |
|          | Vitamin B12 abnormal                | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Vitamin B12 decreased               | 2                                                                       | 2          | 1           | 3          | 5                 | 0                                                              | 0          |
|          | Vitamin B12 increased               | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Vitamin B12 normal                  | 8                                                                       | 8          | 0           | 0          | 8                 | 0                                                              | 0          |
|          | Vitamin B6 normal                   | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Vitamin C decreased                 | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Vitamin D                           | 2                                                                       | 2          | 4           | 5          | 7                 | 0                                                              | 0          |
|          | Vitamin D decreased                 | 3                                                                       | 3          | 5           | 9          | 12                | 0                                                              | 0          |
|          | Vitamin D increased                 | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Vitamin K decreased                 | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Volume blood decreased              | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Waist circumference increased       | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Walking distance test abnormal      | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Wall motion score index abnormal    | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Weight decreased                    | 132                                                                     | 172        | 219         | 488        | 660               | 0                                                              | 0          |
|          | Weight increased                    | 33                                                                      | 48         | 49          | 114        | 162               | 0                                                              | 0          |
|          | West Nile virus test negative       | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | White blood cell count              | 4                                                                       | 4          | 1           | 3          | 7                 | 0                                                              | 0          |
|          | White blood cell count abnormal     | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | White blood cell count decreased    | 18                                                                      | 25         | 17          | 30         | 55                | 0                                                              | 0          |
|          | White blood cell count increased    | 81                                                                      | 104        | 16          | 49         | 153               | 0                                                              | 0          |
|          | White blood cell count normal       | 57                                                                      | 58         | 3           | 4          | 62                | 0                                                              | 0          |
|          | White blood cell morphology normal  | 2                                                                       | 2          | 1           | 1          | 3                 | 0                                                              | 0          |
|          | White blood cells urine             | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | White blood cells urine negative    | 3                                                                       | 3          | 1           | 1          | 4                 | 0                                                              | 0          |
|          | White blood cells urine positive    | 8                                                                       | 8          | 1           | 2          | 10                | 0                                                              | 0          |
|          | Whole body scan                     | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | X-ray                               | 53                                                                      | 53         | 25          | 31         | 84                | 0                                                              | 0          |
|          | X-ray abnormal                      | 6                                                                       | 6          | 4           | 4          | 10                | 0                                                              | 0          |
|          | X-ray dental                        | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | X-ray dental abnormal               | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | X-ray limb                          | 2                                                                       | 2          | 2           | 4          | 6                 | 0                                                              | 0          |
|          | X-ray limb abnormal                 | 7                                                                       | 7          | 1           | 2          | 9                 | 0                                                              | 0          |

|                                    |                                      | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|------------------------------------|--------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|                                    |                                      | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM                           | PT                                   | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|                                    | X-ray limb normal                    | 3                                                                       | 3          | 1           | 3          | 6                 | 0                                                              | 0          |
|                                    | X-ray normal                         | 8                                                                       | 8          | 8           | 10         | 18                | 0                                                              | 0          |
|                                    | X-ray of pelvis and hip              | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|                                    | X-ray of pelvis and hip normal       | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|                                    | X-ray with contrast                  | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                    | Xanthochromia                        | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                    | Yersinia test negative               | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                                    | pH body fluid abnormal               | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                    | pH urine                             | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|                                    | pH urine increased                   | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                    | pH urine normal                      | 4                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
| Metabolism and nutrition disorders | *** SOC TOTAL ***                    | 2130                                                                    | 3242       | 2062        | 7146       | 10388             | 0                                                              | 0          |
|                                    | Abnormal loss of weight              | 18                                                                      | 24         | 14          | 32         | 56                | 0                                                              | 0          |
|                                    | Abnormal weight gain                 | 4                                                                       | 5          | 2           | 6          | 11                | 0                                                              | 0          |
|                                    | Acidosis                             | 18                                                                      | 24         | 0           | 4          | 28                | 0                                                              | 0          |
|                                    | Adult failure to thrive              | 6                                                                       | 9          | 0           | 0          | 9                 | 0                                                              | 0          |
|                                    | Alcohol intolerance                  | 2                                                                       | 2          | 6           | 9          | 11                | 0                                                              | 0          |
|                                    | Apoptosis                            | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                    | Appetite disorder                    | 5                                                                       | 6          | 14          | 50         | 56                | 0                                                              | 0          |
|                                    | Body fat disorder                    | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|                                    | Cachexia                             | 2                                                                       | 9          | 0           | 0          | 9                 | 0                                                              | 0          |
|                                    | Cell death                           | 3                                                                       | 4          | 1           | 1          | 5                 | 0                                                              | 0          |
|                                    | Central obesity                      | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                    | Cholesterosis                        | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|                                    | Copper deficiency                    | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|                                    | Dairy intolerance                    | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|                                    | Dawn phenomenon                      | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|                                    | Decreased appetite                   | 815                                                                     | 1113       | 1401        | 5065       | 6178              | 0                                                              | 0          |
|                                    | Decreased insulin requirement        | 0                                                                       | 0          | 3           | 3          | 3                 | 0                                                              | 0          |
|                                    | Dehydration                          | 236                                                                     | 403        | 127         | 626        | 1029              | 0                                                              | 0          |
|                                    | Diabetes mellitus                    | 51                                                                      | 98         | 2           | 9          | 107               | 0                                                              | 0          |
|                                    | Diabetes mellitus inadequate control | 26                                                                      | 43         | 5           | 5          | 48                | 0                                                              | 0          |
|                                    | Diabetic complication                | 0                                                                       | 1          | 1           | 2          | 3                 | 0                                                              | 0          |
|                                    | Diabetic ketoacidosis                | 43                                                                      | 70         | 0           | 0          | 70                | 0                                                              | 0          |
|                                    | Diabetic metabolic decompensation    | 3                                                                       | 6          | 0           | 0          | 6                 | 0                                                              | 0          |
|                                    | Diet refusal                         | 1                                                                       | 4          | 0           | 5          | 9                 | 0                                                              | 0          |
|                                    | Dyslipidaemia                        | 2                                                                       | 6          | 3           | 4          | 10                | 0                                                              | 0          |
|                                    | Eating disorder symptom              | 0                                                                       | 1          | 2           | 11         | 12                | 0                                                              | 0          |
|                                    | Electrolyte depletion                | 2                                                                       | 2          | 1           | 1          | 3                 | 0                                                              | 0          |
|                                    | Electrolyte imbalance                | 12                                                                      | 18         | 8           | 14         | 32                | 0                                                              | 0          |
|                                    | Enzyme abnormality                   | 0                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|                                    | Failure to thrive                    | 8                                                                       | 11         | 1           | 1          | 12                | 0                                                              | 0          |
|                                    | Feeding disorder                     | 98                                                                      | 145        | 156         | 458        | 603               | 0                                                              | 0          |
|                                    | Feeding intolerance                  | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|                                    | Fluid imbalance                      | 2                                                                       | 3          | 0           | 1          | 4                 | 0                                                              | 0          |
|                                    | Fluid intake reduced                 | 18                                                                      | 34         | 5           | 24         | 58                | 0                                                              | 0          |
|                                    | Fluid retention                      | 37                                                                      | 52         | 31          | 87         | 139               | 0                                                              | 0          |
|                                    | Folate deficiency                    | 2                                                                       | 2          | 1           | 1          | 3                 | 0                                                              | 0          |
|                                    | Food aversion                        | 5                                                                       | 5          | 9           | 18         | 23                | 0                                                              | 0          |

|          |                                            | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|--------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                            | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                         | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Food craving                               | 2                                                                       | 2          | 5           | 11         | 13                | 0                                                              | 0          |
|          | Food intolerance                           | 4                                                                       | 5          | 8           | 24         | 29                | 0                                                              | 0          |
|          | Food refusal                               | 5                                                                       | 11         | 1           | 11         | 22                | 0                                                              | 0          |
|          | Fructose intolerance                       | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Glucose tolerance impaired                 | 0                                                                       | 1          | 3           | 10         | 11                | 0                                                              | 0          |
|          | Gluten sensitivity                         | 2                                                                       | 2          | 2           | 3          | 5                 | 0                                                              | 0          |
|          | Gout                                       | 36                                                                      | 53         | 46          | 148        | 201               | 0                                                              | 0          |
|          | Haemochromatosis                           | 1                                                                       | 1          | 3           | 3          | 4                 | 0                                                              | 0          |
|          | Histamine intolerance                      | 3                                                                       | 3          | 6           | 8          | 11                | 0                                                              | 0          |
|          | Hyperammonaemia                            | 2                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Hypercalcaemia                             | 4                                                                       | 10         | 1           | 1          | 11                | 0                                                              | 0          |
|          | Hyperchloraemia                            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Hypercholesterolaemia                      | 0                                                                       | 2          | 2           | 4          | 6                 | 0                                                              | 0          |
|          | Hyperferritinaemia                         | 0                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Hyperglycaemia                             | 48                                                                      | 80         | 24          | 89         | 169               | 0                                                              | 0          |
|          | Hyperglycaemic hyperosmolar nonketotic s   | 4                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Hyperkalaemia                              | 41                                                                      | 65         | 0           | 0          | 65                | 0                                                              | 0          |
|          | Hyperlipasaemia                            | 2                                                                       | 2          | 2           | 2          | 4                 | 0                                                              | 0          |
|          | Hyperlipidaemia                            | 15                                                                      | 23         | 2           | 10         | 33                | 0                                                              | 0          |
|          | Hypermagnesaemia                           | 0                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Hypermetabolism                            | 0                                                                       | 0          | 2           | 3          | 3                 | 0                                                              | 0          |
|          | Hypernatraemia                             | 10                                                                      | 14         | 0           | 0          | 14                | 0                                                              | 0          |
|          | Hyperphagia                                | 5                                                                       | 6          | 2           | 5          | 11                | 0                                                              | 0          |
|          | Hyperphosphataemia                         | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Hyperproteinaemia                          | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Hypertriglyceridaemia                      | 3                                                                       | 7          | 2           | 2          | 9                 | 0                                                              | 0          |
|          | Hyperuricaemia                             | 0                                                                       | 2          | 1           | 2          | 4                 | 0                                                              | 0          |
|          | Hypervolaemia                              | 31                                                                      | 51         | 3           | 6          | 57                | 0                                                              | 0          |
|          | Hypoalbuminaemia                           | 8                                                                       | 10         | 0           | 2          | 12                | 0                                                              | 0          |
|          | Hypocalcaemia                              | 7                                                                       | 10         | 0           | 3          | 13                | 0                                                              | 0          |
|          | Hypochloraemia                             | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Hypoglycaemia                              | 30                                                                      | 52         | 34          | 80         | 132               | 0                                                              | 0          |
|          | Hypoglycaemia neonatal                     | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Hypokalaemia                               | 50                                                                      | 104        | 3           | 6          | 110               | 0                                                              | 0          |
|          | Hypokalaemic syndrome                      | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Hypomagnesaemia                            | 12                                                                      | 22         | 0           | 1          | 23                | 0                                                              | 0          |
|          | Hypometabolism                             | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Hyponatraemia                              | 80                                                                      | 123        | 7           | 19         | 142               | 0                                                              | 0          |
|          | Hypoosmolar state                          | 6                                                                       | 8          | 0           | 0          | 8                 | 0                                                              | 0          |
|          | Hypophagia                                 | 90                                                                      | 143        | 15          | 40         | 183               | 0                                                              | 0          |
|          | Hypophosphataemia                          | 1                                                                       | 2          | 0           | 1          | 3                 | 0                                                              | 0          |
|          | Hypovitaminosis                            | 2                                                                       | 3          | 1           | 4          | 7                 | 0                                                              | 0          |
|          | Hypovolaemia                               | 9                                                                       | 15         | 5           | 5          | 20                | 0                                                              | 0          |
|          | Increased appetite                         | 7                                                                       | 7          | 23          | 47         | 54                | 0                                                              | 0          |
|          | Increased insulin requirement              | 0                                                                       | 2          | 2           | 7          | 9                 | 0                                                              | 0          |
|          | Insulin resistance                         | 2                                                                       | 3          | 1           | 3          | 6                 | 0                                                              | 0          |
|          | Insulin resistant diabetes                 | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Insulin-requiring type 2 diabetes mellitus | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Iron deficiency                            | 3                                                                       | 3          | 1           | 6          | 9                 | 0                                                              | 0          |

|                                                 |                                            | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|-------------------------------------------------|--------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|                                                 |                                            | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM                                        | PT                                         | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|                                                 | Iron metabolism disorder                   | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|                                                 | Ketoacidosis                               | 4                                                                       | 9          | 0           | 0          | 9                 | 0                                                              | 0          |
|                                                 | Lack of satiety                            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                                 | Lactic acidosis                            | 34                                                                      | 63         | 1           | 1          | 64                | 0                                                              | 0          |
|                                                 | Lactose intolerance                        | 0                                                                       | 1          | 2           | 5          | 6                 | 0                                                              | 0          |
|                                                 | Latent autoimmune diabetes in adults       | 1                                                                       | 1          | 1           | 2          | 3                 | 0                                                              | 0          |
|                                                 | Lipoedema                                  | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                                 | Lipomatosis                                | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|                                                 | Magnesium deficiency                       | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                                 | Malnutrition                               | 13                                                                      | 18         | 0           | 4          | 22                | 0                                                              | 0          |
|                                                 | Metabolic acidosis                         | 22                                                                      | 37         | 1           | 4          | 41                | 0                                                              | 0          |
|                                                 | Metabolic alkalosis                        | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                                                 | Metabolic disorder                         | 4                                                                       | 5          | 1           | 3          | 8                 | 0                                                              | 0          |
|                                                 | Mineral deficiency                         | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                                                 | Neonatal insufficient breast milk syndrome | 2                                                                       | 4          | 2           | 2          | 6                 | 0                                                              | 0          |
|                                                 | Obesity                                    | 19                                                                      | 23         | 2           | 7          | 30                | 0                                                              | 0          |
|                                                 | Oligodipsia                                | 2                                                                       | 2          | 1           | 2          | 4                 | 0                                                              | 0          |
|                                                 | Overweight                                 | 1                                                                       | 1          | 1           | 6          | 7                 | 0                                                              | 0          |
|                                                 | Oxidative stress                           | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                                 | Periarthritis calcarea                     | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|                                                 | Polydipsia                                 | 4                                                                       | 6          | 13          | 24         | 30                | 0                                                              | 0          |
|                                                 | Poor feeding infant                        | 1                                                                       | 1          | 3           | 7          | 8                 | 0                                                              | 0          |
|                                                 | Postprandial hypoglycaemia                 | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|                                                 | Protein deficiency                         | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|                                                 | Pseudohyponatraemia                        | 0                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                                                 | Salt craving                               | 1                                                                       | 1          | 1           | 7          | 8                 | 0                                                              | 0          |
|                                                 | Shock hypoglycaemic                        | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                                 | Starvation                                 | 2                                                                       | 2          | 0           | 2          | 4                 | 0                                                              | 0          |
|                                                 | Steroid diabetes                           | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                                 | Tetany                                     | 6                                                                       | 8          | 6           | 12         | 20                | 0                                                              | 0          |
|                                                 | Type 1 diabetes mellitus                   | 22                                                                      | 27         | 1           | 2          | 29                | 0                                                              | 0          |
|                                                 | Type 2 diabetes mellitus                   | 21                                                                      | 31         | 0           | 0          | 31                | 0                                                              | 0          |
|                                                 | Underweight                                | 0                                                                       | 0          | 1           | 3          | 3                 | 0                                                              | 0          |
|                                                 | Vitamin B complex deficiency               | 0                                                                       | 0          | 0           | 3          | 3                 | 0                                                              | 0          |
|                                                 | Vitamin B12 deficiency                     | 3                                                                       | 7          | 7           | 7          | 14                | 0                                                              | 0          |
|                                                 | Vitamin D deficiency                       | 3                                                                       | 7          | 4           | 11         | 18                | 0                                                              | 0          |
|                                                 | Weight fluctuation                         | 0                                                                       | 1          | 3           | 6          | 7                 | 0                                                              | 0          |
|                                                 | Weight gain poor                           | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|                                                 | Weight loss poor                           | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
| Musculoskeletal and connective tissue disorders | *** SOC TOTAL ***                          | 16390                                                                   | 22224      | 59672       | 149206     | 171430            | 0                                                              | 0          |
|                                                 | Amplified musculoskeletal pain syndrome    | 0                                                                       | 0          | 1           | 3          | 3                 | 0                                                              | 0          |
|                                                 | Amyotrophy                                 | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|                                                 | Ankle deformity                            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                                 | Ankylosing spondylitis                     | 14                                                                      | 20         | 2           | 2          | 22                | 0                                                              | 0          |
|                                                 | Arthralgia                                 | 3076                                                                    | 3859       | 12470       | 28717      | 32576             | 0                                                              | 0          |
|                                                 | Arthritis                                  | 105                                                                     | 144        | 360         | 733        | 877               | 0                                                              | 0          |
|                                                 | Arthritis allergic                         | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|                                                 | Arthritis enteropathic                     | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|                                                 | Arthritis reactive                         | 32                                                                      | 46         | 5           | 7          | 53                | 0                                                              | 0          |

|          |                                           | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|-------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                           | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                        | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Arthropathy                               | 14                                                                      | 18         | 36          | 65         | 83                | 0                                                              | 0          |
|          | Autoimmune arthritis                      | 1                                                                       | 2          | 1           | 1          | 3                 | 0                                                              | 0          |
|          | Autoimmune myositis                       | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Axial spondyloarthritis                   | 0                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Axillary mass                             | 39                                                                      | 46         | 98          | 276        | 322               | 0                                                              | 0          |
|          | Back disorder                             | 2                                                                       | 3          | 8           | 16         | 19                | 0                                                              | 0          |
|          | Back pain                                 | 931                                                                     | 1242       | 1662        | 5001       | 6243              | 0                                                              | 0          |
|          | Bone cyst                                 | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Bone demineralisation                     | 1                                                                       | 1          | 1           | 2          | 3                 | 0                                                              | 0          |
|          | Bone disorder                             | 2                                                                       | 2          | 1           | 8          | 10                | 0                                                              | 0          |
|          | Bone erosion                              | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Bone hypertrophy                          | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Bone infarction                           | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Bone lesion                               | 3                                                                       | 3          | 1           | 1          | 4                 | 0                                                              | 0          |
|          | Bone pain                                 | 123                                                                     | 160        | 443         | 1209       | 1369              | 0                                                              | 0          |
|          | Bone swelling                             | 1                                                                       | 1          | 6           | 19         | 20                | 0                                                              | 0          |
|          | Bursa disorder                            | 2                                                                       | 2          | 4           | 7          | 9                 | 0                                                              | 0          |
|          | Bursal fluid accumulation                 | 1                                                                       | 2          | 1           | 3          | 5                 | 0                                                              | 0          |
|          | Bursitis                                  | 42                                                                      | 57         | 58          | 147        | 204               | 0                                                              | 0          |
|          | Camptocormia                              | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Cervical spinal stenosis                  | 4                                                                       | 10         | 0           | 0          | 10                | 0                                                              | 0          |
|          | Chest wall cyst                           | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Chest wall haematoma                      | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Chest wall mass                           | 1                                                                       | 1          | 1           | 3          | 4                 | 0                                                              | 0          |
|          | Chondritis                                | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Chondrocalcinosis                         | 2                                                                       | 2          | 2           | 3          | 5                 | 0                                                              | 0          |
|          | Chondrocalcinosis pyrophosphate           | 2                                                                       | 4          | 4           | 7          | 11                | 0                                                              | 0          |
|          | Chondropathy                              | 0                                                                       | 0          | 2           | 3          | 3                 | 0                                                              | 0          |
|          | Chronic kidney disease-mineral and bone d | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Clubbing                                  | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Coccydynia                                | 4                                                                       | 5          | 4           | 10         | 15                | 0                                                              | 0          |
|          | Collagen disorder                         | 2                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Collagen-vascular disease                 | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Compartment syndrome                      | 2                                                                       | 7          | 0           | 0          | 7                 | 0                                                              | 0          |
|          | Connective tissue disorder                | 6                                                                       | 6          | 7           | 14         | 20                | 0                                                              | 0          |
|          | Connective tissue inflammation            | 0                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Costochondritis                           | 17                                                                      | 21         | 17          | 38         | 59                | 0                                                              | 0          |
|          | Dactylitis                                | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|          | Decreased nasolabial fold                 | 0                                                                       | 1          | 0           | 3          | 4                 | 0                                                              | 0          |
|          | Drooping shoulder syndrome                | 1                                                                       | 1          | 1           | 2          | 3                 | 0                                                              | 0          |
|          | Dupuytren's contracture                   | 6                                                                       | 13         | 0           | 0          | 13                | 0                                                              | 0          |
|          | Dysponosis                                | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Eagle's syndrome                          | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Elbow deformity                           | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Enthesopathy                              | 2                                                                       | 3          | 1           | 2          | 5                 | 0                                                              | 0          |
|          | Exostosis                                 | 3                                                                       | 4          | 3           | 5          | 9                 | 0                                                              | 0          |
|          | Extremity contracture                     | 2                                                                       | 4          | 3           | 11         | 15                | 0                                                              | 0          |
|          | Facet joint syndrome                      | 6                                                                       | 9          | 2           | 2          | 11                | 0                                                              | 0          |
|          | Facial asymmetry                          | 9                                                                       | 13         | 9           | 21         | 34                | 0                                                              | 0          |

|          |                                     | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|-------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                     | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                  | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Fasciitis                           | 3                                                                       | 4          | 1           | 1          | 5                 | 0                                                              | 0          |
|          | Femoroacetabular impingement        | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Fibromyalgia                        | 33                                                                      | 40         | 65          | 148        | 188               | 0                                                              | 0          |
|          | Finger deformity                    | 1                                                                       | 2          | 2           | 7          | 9                 | 0                                                              | 0          |
|          | Fistula                             | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Fistula discharge                   | 0                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Flank pain                          | 59                                                                      | 98         | 57          | 169        | 267               | 0                                                              | 0          |
|          | Fluctuance                          | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Foot deformity                      | 1                                                                       | 3          | 3           | 11         | 14                | 0                                                              | 0          |
|          | Fracture pain                       | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|          | Gouty arthritis                     | 1                                                                       | 1          | 1           | 2          | 3                 | 0                                                              | 0          |
|          | Gouty tophus                        | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Groin pain                          | 38                                                                      | 55         | 71          | 161        | 216               | 0                                                              | 0          |
|          | Growing pains                       | 17                                                                      | 17         | 15          | 16         | 33                | 0                                                              | 0          |
|          | Growth accelerated                  | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Growth retardation                  | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Haemarthrosis                       | 2                                                                       | 4          | 0           | 1          | 5                 | 0                                                              | 0          |
|          | Haematoma muscle                    | 5                                                                       | 8          | 1           | 2          | 10                | 0                                                              | 0          |
|          | Hand deformity                      | 1                                                                       | 2          | 6           | 13         | 15                | 0                                                              | 0          |
|          | Hip deformity                       | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Hypermobility syndrome              | 1                                                                       | 2          | 1           | 2          | 4                 | 0                                                              | 0          |
|          | Immune-mediated myositis            | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Inguinal mass                       | 1                                                                       | 1          | 2           | 2          | 3                 | 0                                                              | 0          |
|          | Intervertebral disc annular tear    | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Intervertebral disc compression     | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Intervertebral disc degeneration    | 17                                                                      | 28         | 4           | 16         | 44                | 0                                                              | 0          |
|          | Intervertebral disc disorder        | 3                                                                       | 7          | 2           | 7          | 14                | 0                                                              | 0          |
|          | Intervertebral disc displacement    | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Intervertebral disc protrusion      | 17                                                                      | 27         | 12          | 22         | 49                | 0                                                              | 0          |
|          | Intervertebral disc space narrowing | 3                                                                       | 6          | 2           | 3          | 9                 | 0                                                              | 0          |
|          | Jaw clicking                        | 1                                                                       | 1          | 0           | 5          | 6                 | 0                                                              | 0          |
|          | Jaw cyst                            | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Jaw disorder                        | 8                                                                       | 10         | 5           | 23         | 33                | 0                                                              | 0          |
|          | Joint adhesion                      | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Joint ankylosis                     | 1                                                                       | 2          | 3           | 3          | 5                 | 0                                                              | 0          |
|          | Joint contracture                   | 4                                                                       | 7          | 2           | 7          | 14                | 0                                                              | 0          |
|          | Joint destruction                   | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Joint effusion                      | 15                                                                      | 20         | 6           | 20         | 40                | 0                                                              | 0          |
|          | Joint hyperextension                | 0                                                                       | 0          | 1           | 4          | 4                 | 0                                                              | 0          |
|          | Joint instability                   | 2                                                                       | 5          | 0           | 6          | 11                | 0                                                              | 0          |
|          | Joint lock                          | 10                                                                      | 14         | 14          | 31         | 45                | 0                                                              | 0          |
|          | Joint noise                         | 6                                                                       | 6          | 9           | 27         | 33                | 0                                                              | 0          |
|          | Joint range of motion decreased     | 51                                                                      | 86         | 54          | 409        | 495               | 0                                                              | 0          |
|          | Joint space narrowing               | 3                                                                       | 4          | 0           | 1          | 5                 | 0                                                              | 0          |
|          | Joint stiffness                     | 89                                                                      | 113        | 121         | 392        | 505               | 0                                                              | 0          |
|          | Joint swelling                      | 163                                                                     | 219        | 348         | 1126       | 1345              | 0                                                              | 0          |
|          | Joint vibration                     | 0                                                                       | 1          | 0           | 4          | 5                 | 0                                                              | 0          |
|          | Joint warmth                        | 3                                                                       | 6          | 9           | 25         | 31                | 0                                                              | 0          |
|          | Juvenile idiopathic arthritis       | 3                                                                       | 3          | 0           | 1          | 4                 | 0                                                              | 0          |



|          |                                 | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|---------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                 | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                              | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Knee deformity                  | 0                                                                       | 0          | 2           | 5          | 5                 | 0                                                              | 0          |
|          | Kyphoscoliosis                  | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Kyphosis                        | 1                                                                       | 1          | 2           | 4          | 5                 | 0                                                              | 0          |
|          | Ligament pain                   | 0                                                                       | 0          | 3           | 9          | 9                 | 0                                                              | 0          |
|          | Ligamentitis                    | 2                                                                       | 2          | 2           | 2          | 4                 | 0                                                              | 0          |
|          | Limb deformity                  | 1                                                                       | 1          | 1           | 5          | 6                 | 0                                                              | 0          |
|          | Limb discomfort                 | 349                                                                     | 470        | 3248        | 5167       | 5637              | 0                                                              | 0          |
|          | Limb mass                       | 8                                                                       | 12         | 23          | 100        | 112               | 0                                                              | 0          |
|          | Loose body in joint             | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Lordosis                        | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Lumbar spinal stenosis          | 2                                                                       | 2          | 1           | 2          | 4                 | 0                                                              | 0          |
|          | Lupus-like syndrome             | 6                                                                       | 10         | 1           | 1          | 11                | 0                                                              | 0          |
|          | Mandibular mass                 | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Mastication disorder            | 4                                                                       | 7          | 15          | 63         | 70                | 0                                                              | 0          |
|          | Masticatory pain                | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Medial tibial stress syndrome   | 1                                                                       | 1          | 1           | 7          | 8                 | 0                                                              | 0          |
|          | Metatarsalgia                   | 0                                                                       | 0          | 2           | 3          | 3                 | 0                                                              | 0          |
|          | Mixed connective tissue disease | 5                                                                       | 9          | 0           | 0          | 9                 | 0                                                              | 0          |
|          | Mobility decreased              | 271                                                                     | 559        | 635         | 2938       | 3497              | 0                                                              | 0          |
|          | Morphoea                        | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Muscle atrophy                  | 16                                                                      | 27         | 22          | 35         | 62                | 0                                                              | 0          |
|          | Muscle contracture              | 9                                                                       | 15         | 8           | 24         | 39                | 0                                                              | 0          |
|          | Muscle discomfort               | 6                                                                       | 6          | 54          | 117        | 123               | 0                                                              | 0          |
|          | Muscle disorder                 | 11                                                                      | 13         | 14          | 39         | 52                | 0                                                              | 0          |
|          | Muscle fatigue                  | 68                                                                      | 84         | 60          | 188        | 272               | 0                                                              | 0          |
|          | Muscle haemorrhage              | 2                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Muscle hypertrophy              | 0                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Muscle mass                     | 1                                                                       | 1          | 1           | 6          | 7                 | 0                                                              | 0          |
|          | Muscle oedema                   | 4                                                                       | 6          | 2           | 3          | 9                 | 0                                                              | 0          |
|          | Muscle rigidity                 | 28                                                                      | 46         | 41          | 117        | 163               | 0                                                              | 0          |
|          | Muscle spasms                   | 500                                                                     | 641        | 940         | 2657       | 3298              | 0                                                              | 0          |
|          | Muscle swelling                 | 11                                                                      | 17         | 25          | 106        | 123               | 0                                                              | 0          |
|          | Muscle tightness                | 39                                                                      | 77         | 192         | 664        | 741               | 0                                                              | 0          |
|          | Muscle twitching                | 99                                                                      | 145        | 248         | 654        | 799               | 0                                                              | 0          |
|          | Muscular weakness               | 698                                                                     | 1036       | 1121        | 2619       | 3655              | 0                                                              | 0          |
|          | Musculoskeletal chest pain      | 99                                                                      | 129        | 144         | 380        | 509               | 0                                                              | 0          |
|          | Musculoskeletal discomfort      | 33                                                                      | 59         | 172         | 543        | 602               | 0                                                              | 0          |
|          | Musculoskeletal disorder        | 21                                                                      | 38         | 19          | 44         | 82                | 0                                                              | 0          |
|          | Musculoskeletal pain            | 147                                                                     | 165        | 485         | 791        | 956               | 0                                                              | 0          |
|          | Musculoskeletal stiffness       | 435                                                                     | 577        | 752         | 2678       | 3255              | 0                                                              | 0          |
|          | Myalgia                         | 3809                                                                    | 4853       | 23023       | 49275      | 54128             | 0                                                              | 0          |
|          | Myalgia intercostal             | 0                                                                       | 0          | 0           | 3          | 3                 | 0                                                              | 0          |
|          | Myofascial pain syndrome        | 2                                                                       | 2          | 0           | 2          | 4                 | 0                                                              | 0          |
|          | Myokymia                        | 0                                                                       | 0          | 3           | 5          | 5                 | 0                                                              | 0          |
|          | Myopathy                        | 6                                                                       | 8          | 4           | 11         | 19                | 0                                                              | 0          |
|          | Myosclerosis                    | 3                                                                       | 26         | 1           | 6          | 32                | 0                                                              | 0          |
|          | Myositis                        | 26                                                                      | 41         | 41          | 73         | 114               | 0                                                              | 0          |
|          | Neck mass                       | 12                                                                      | 16         | 32          | 95         | 111               | 0                                                              | 0          |
|          | Neck pain                       | 485                                                                     | 666        | 1013        | 3867       | 4533              | 0                                                              | 0          |

|          |                              | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                              | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                           | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Neuropathic arthropathy      | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Neuropathic muscular atrophy | 2                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Nose deformity               | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|          | Nuchal rigidity              | 6                                                                       | 10         | 24          | 46         | 56                | 0                                                              | 0          |
|          | Oligoarthritis               | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Osteitis                     | 1                                                                       | 1          | 5           | 12         | 13                | 0                                                              | 0          |
|          | Osteitis deformans           | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Osteoarthritis               | 26                                                                      | 42         | 35          | 71         | 113               | 0                                                              | 0          |
|          | Osteolysis                   | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Osteonecrosis of jaw         | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Osteopenia                   | 2                                                                       | 5          | 0           | 1          | 6                 | 0                                                              | 0          |
|          | Osteoporosis                 | 3                                                                       | 5          | 2           | 6          | 11                | 0                                                              | 0          |
|          | Osteosclerosis               | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Pain in extremity            | 3287                                                                    | 4467       | 10490       | 34806      | 39273             | 0                                                              | 0          |
|          | Pain in jaw                  | 94                                                                      | 142        | 174         | 670        | 812               | 0                                                              | 0          |
|          | Palindromic rheumatism       | 2                                                                       | 2          | 1           | 1          | 3                 | 0                                                              | 0          |
|          | Periarthritis                | 58                                                                      | 75         | 113         | 206        | 281               | 0                                                              | 0          |
|          | Periarticular disorder       | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Periostitis                  | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Plantar fascial fibromatosis | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|          | Plantar fasciitis            | 2                                                                       | 3          | 9           | 19         | 22                | 0                                                              | 0          |
|          | Polyarthritis                | 23                                                                      | 37         | 4           | 4          | 41                | 0                                                              | 0          |
|          | Polychondritis               | 4                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Polymyalgia rheumatica       | 73                                                                      | 139        | 7           | 12         | 151               | 0                                                              | 0          |
|          | Polymyositis                 | 4                                                                       | 7          | 1           | 2          | 9                 | 0                                                              | 0          |
|          | Posture abnormal             | 12                                                                      | 34         | 8           | 53         | 87                | 0                                                              | 0          |
|          | Pseudarthrosis               | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Psoriatic arthropathy        | 12                                                                      | 27         | 2           | 3          | 30                | 0                                                              | 0          |
|          | Pubic pain                   | 0                                                                       | 0          | 1           | 3          | 3                 | 0                                                              | 0          |
|          | Purple glove syndrome        | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Resorption bone increased    | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|          | Reynold's syndrome           | 0                                                                       | 2          | 1           | 1          | 3                 | 0                                                              | 0          |
|          | Rhabdomyolysis               | 63                                                                      | 124        | 1           | 2          | 126               | 0                                                              | 0          |
|          | Rheumatic disorder           | 3                                                                       | 4          | 15          | 20         | 24                | 0                                                              | 0          |
|          | Rheumatoid arthritis         | 148                                                                     | 282        | 23          | 43         | 325               | 0                                                              | 0          |
|          | Rheumatoid nodule            | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Rotator cuff syndrome        | 12                                                                      | 20         | 21          | 54         | 74                | 0                                                              | 0          |
|          | Sacral pain                  | 1                                                                       | 1          | 3           | 8          | 9                 | 0                                                              | 0          |
|          | Sacroiliac joint dysfunction | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Sacroiliitis                 | 1                                                                       | 1          | 1           | 2          | 3                 | 0                                                              | 0          |
|          | Sarcopenia                   | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Scleroderma                  | 1                                                                       | 6          | 1           | 1          | 7                 | 0                                                              | 0          |
|          | Scoliosis                    | 6                                                                       | 7          | 0           | 1          | 8                 | 0                                                              | 0          |
|          | Seronegative arthritis       | 2                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Shoulder deformity           | 1                                                                       | 1          | 1           | 2          | 3                 | 0                                                              | 0          |
|          | Sjogren's syndrome           | 8                                                                       | 15         | 0           | 2          | 17                | 0                                                              | 0          |
|          | Soft tissue disorder         | 2                                                                       | 2          | 0           | 2          | 4                 | 0                                                              | 0          |
|          | Soft tissue haemorrhage      | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Soft tissue mass             | 1                                                                       | 1          | 4           | 9          | 10                | 0                                                              | 0          |

|                                                   |                                            | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|---------------------------------------------------|--------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|                                                   |                                            | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM                                          | PT                                         | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|                                                   | Soft tissue necrosis                       | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                                                   | Soft tissue swelling                       | 6                                                                       | 8          | 2           | 13         | 21                | 0                                                              | 0          |
|                                                   | Somatic dysfunction                        | 0                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|                                                   | Spinal deformity                           | 2                                                                       | 5          | 0           | 1          | 6                 | 0                                                              | 0          |
|                                                   | Spinal disorder                            | 2                                                                       | 8          | 3           | 4          | 12                | 0                                                              | 0          |
|                                                   | Spinal flattening                          | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                                   | Spinal fusion acquired                     | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|                                                   | Spinal osteoarthritis                      | 21                                                                      | 31         | 8           | 11         | 42                | 0                                                              | 0          |
|                                                   | Spinal pain                                | 34                                                                      | 47         | 84          | 231        | 278               | 0                                                              | 0          |
|                                                   | Spinal retrolisthesis                      | 3                                                                       | 4          | 0           | 1          | 5                 | 0                                                              | 0          |
|                                                   | Spinal stenosis                            | 8                                                                       | 17         | 3           | 7          | 24                | 0                                                              | 0          |
|                                                   | Spinal synovial cyst                       | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|                                                   | Spondylitis                                | 7                                                                       | 8          | 6           | 19         | 27                | 0                                                              | 0          |
|                                                   | Spondyloarthropathy                        | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                                   | Spondylolisthesis                          | 5                                                                       | 7          | 0           | 1          | 8                 | 0                                                              | 0          |
|                                                   | Still's disease                            | 4                                                                       | 5          | 0           | 1          | 6                 | 0                                                              | 0          |
|                                                   | Symphysiolysis                             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                                   | Synovial cyst                              | 9                                                                       | 10         | 21          | 43         | 53                | 0                                                              | 0          |
|                                                   | Synovial disorder                          | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|                                                   | Synovitis                                  | 4                                                                       | 6          | 3           | 13         | 19                | 0                                                              | 0          |
|                                                   | Systemic lupus erythematosus               | 42                                                                      | 93         | 6           | 11         | 104               | 0                                                              | 0          |
|                                                   | Systemic scleroderma                       | 1                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|                                                   | Temporomandibular joint syndrome           | 2                                                                       | 4          | 19          | 46         | 50                | 0                                                              | 0          |
|                                                   | Tendinous contracture                      | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                                   | Tendon calcification                       | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|                                                   | Tendon discomfort                          | 1                                                                       | 1          | 7           | 13         | 14                | 0                                                              | 0          |
|                                                   | Tendon disorder                            | 11                                                                      | 13         | 5           | 14         | 27                | 0                                                              | 0          |
|                                                   | Tendon laxity                              | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|                                                   | Tendon pain                                | 14                                                                      | 15         | 18          | 53         | 68                | 0                                                              | 0          |
|                                                   | Tendon sheath disorder                     | 0                                                                       | 0          | 2           | 2          | 2                 | 0                                                              | 0          |
|                                                   | Tendonitis                                 | 20                                                                      | 27         | 52          | 106        | 133               | 0                                                              | 0          |
|                                                   | Tenosynovitis                              | 1                                                                       | 2          | 5           | 5          | 7                 | 0                                                              | 0          |
|                                                   | Tenosynovitis stenosans                    | 0                                                                       | 0          | 2           | 2          | 2                 | 0                                                              | 0          |
|                                                   | Toe walking                                | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|                                                   | Torticollis                                | 9                                                                       | 11         | 13          | 26         | 37                | 0                                                              | 0          |
|                                                   | Trigger finger                             | 8                                                                       | 9          | 13          | 28         | 37                | 0                                                              | 0          |
|                                                   | Trismus                                    | 13                                                                      | 22         | 24          | 86         | 108               | 0                                                              | 0          |
|                                                   | Undifferentiated connective tissue disease | 0                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|                                                   | Vertebral end plate inflammation           | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|                                                   | Vertebral foraminal stenosis               | 9                                                                       | 16         | 2           | 2          | 18                | 0                                                              | 0          |
|                                                   | Vertebral lesion                           | 1                                                                       | 2          | 2           | 2          | 4                 | 0                                                              | 0          |
|                                                   | Vertebral osteophyte                       | 3                                                                       | 3          | 0           | 1          | 4                 | 0                                                              | 0          |
|                                                   | Vertebral wedging                          | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                                   | Weight bearing difficulty                  | 17                                                                      | 33         | 15          | 32         | 65                | 0                                                              | 0          |
|                                                   | Winged scapula                             | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                                   | Wrist deformity                            | 0                                                                       | 0          | 0           | 3          | 3                 | 0                                                              | 0          |
| Neoplasms benign, malignant and unspecified (incl | *** SOC TOTAL ***                          | 456                                                                     | 670        | 93          | 168        | 838               | 0                                                              | 0          |
|                                                   | Abdominal neoplasm                         | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                                                   | Acanthoma                                  | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |

|          |                                          | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                          | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                       | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Acoustic neuroma                         | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Acrochordon                              | 1                                                                       | 1          | 0           | 3          | 4                 | 0                                                              | 0          |
|          | Acute leukaemia                          | 3                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Acute lymphocytic leukaemia              | 5                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Acute monocytic leukaemia                | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Acute myeloid leukaemia                  | 12                                                                      | 20         | 0           | 0          | 20                | 0                                                              | 0          |
|          | Acute myeloid leukaemia recurrent        | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Acute myelomonocytic leukaemia           | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Acute promyelocytic leukaemia            | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Adenocarcinoma                           | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Adenocarcinoma gastric                   | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Adenocarcinoma metastatic                | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Adenocarcinoma of colon                  | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Adenocarcinoma of the cervix             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Adenocarcinoma pancreas                  | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Adrenal adenoma                          | 1                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Adrenal gland cancer                     | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Adrenal neoplasm                         | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|          | Angioimmunoblastic T-cell lymphoma       | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Angioimmunoblastic T-cell lymphoma stage | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Angiolipoma                              | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Angiosarcoma                             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Anogenital warts                         | 1                                                                       | 1          | 1           | 2          | 3                 | 0                                                              | 0          |
|          | B-cell lymphoma                          | 5                                                                       | 9          | 0           | 0          | 9                 | 0                                                              | 0          |
|          | B-cell lymphoma stage II                 | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | B-cell lymphoma stage III                | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | B-cell small lymphocytic lymphoma        | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | B-cell type acute leukaemia              | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Basal cell carcinoma                     | 3                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Benign biliary neoplasm                  | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Benign breast neoplasm                   | 0                                                                       | 0          | 2           | 2          | 2                 | 0                                                              | 0          |
|          | Benign hepatic neoplasm                  | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Benign hydatidiform mole                 | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Benign lymph node neoplasm               | 1                                                                       | 1          | 0           | 3          | 4                 | 0                                                              | 0          |
|          | Benign neoplasm                          | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Benign neoplasm of cervix uteri          | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Benign neoplasm of thyroid gland         | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Benign uterine neoplasm                  | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Bladder cancer                           | 7                                                                       | 7          | 0           | 0          | 7                 | 0                                                              | 0          |
|          | Bladder cancer stage IV                  | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Bladder neoplasm                         | 1                                                                       | 2          | 0           | 1          | 3                 | 0                                                              | 0          |
|          | Bladder transitional cell carcinoma      | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Blast crisis in myelogenous leukaemia    | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Bone cancer                              | 3                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Brain neoplasm                           | 8                                                                       | 11         | 0           | 0          | 11                | 0                                                              | 0          |
|          | Brain neoplasm benign                    | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Breast adenoma                           | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Breast cancer                            | 15                                                                      | 21         | 2           | 3          | 24                | 0                                                              | 0          |
|          | Breast cancer female                     | 15                                                                      | 18         | 1           | 1          | 19                | 0                                                              | 0          |

|          |                                          | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                          | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                       | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Breast cancer metastatic                 | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Breast cancer recurrent                  | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Brenner tumour                           | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Bronchial carcinoma                      | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Burkitt's lymphoma                       | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Castleman's disease                      | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Central nervous system lymphoma          | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Cerebellar tumour                        | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Cerebral haemangioma                     | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Cervix carcinoma                         | 2                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Cholangiocarcinoma                       | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Chondroma                                | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Chronic eosinophilic leukaemia           | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Chronic leukaemia                        | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Chronic lymphocytic leukaemia            | 7                                                                       | 13         | 0           | 0          | 13                | 0                                                              | 0          |
|          | Chronic lymphocytic leukaemia recurrent  | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Chronic myeloid leukaemia                | 4                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Chronic myelomonocytic leukaemia         | 2                                                                       | 3          | 1           | 1          | 4                 | 0                                                              | 0          |
|          | Colon cancer                             | 5                                                                       | 7          | 0           | 0          | 7                 | 0                                                              | 0          |
|          | Colon cancer metastatic                  | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Colon cancer stage IV                    | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Colorectal cancer                        | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Cutaneous T-cell lymphoma                | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Cutaneous lymphoma                       | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Diffuse large B-cell lymphoma            | 2                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Diffuse large B-cell lymphoma stage IV   | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Endometrial adenocarcinoma               | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Endometrial cancer                       | 1                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Essential thrombocythaemia               | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Extradural neoplasm                      | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Extranodal marginal zone B-cell lymphoma | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Eyelid tumour                            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Fallopian tube cancer                    | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Fibroadenoma of breast                   | 0                                                                       | 0          | 2           | 2          | 2                 | 0                                                              | 0          |
|          | Follicular lymphoma                      | 3                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Gastric cancer                           | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Gastric cancer stage I                   | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Gastric cancer stage IV                  | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Germ cell cancer                         | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Glioblastoma                             | 3                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Glioblastoma multiforme                  | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Good syndrome                            | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Haemangioblastoma                        | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Haemangioma                              | 0                                                                       | 1          | 10          | 13         | 14                | 0                                                              | 0          |
|          | Haemangioma of bone                      | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Haemangioma of liver                     | 4                                                                       | 4          | 0           | 1          | 5                 | 0                                                              | 0          |
|          | Haemangioma of skin                      | 0                                                                       | 0          | 7           | 11         | 11                | 0                                                              | 0          |
|          | Haematological malignancy                | 2                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Haematopoietic neoplasm                  | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |

|          |                                              | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|----------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                              | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                           | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Hepatic cancer                               | 4                                                                       | 7          | 0           | 0          | 7                 | 0                                                              | 0          |
|          | Hepatic neoplasm                             | 2                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Hepatocellular carcinoma                     | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Hodgkin's disease                            | 2                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Hodgkin's disease nodular sclerosis stage II | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Hormone receptor positive HER2 negative b    | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Hypergammaglobulinaemia benign monocl        | 3                                                                       | 3          | 1           | 1          | 4                 | 0                                                              | 0          |
|          | Intraductal papillary mucinous neoplasm      | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Intraductal proliferative breast lesion      | 2                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Invasive breast carcinoma                    | 2                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Invasive ductal breast carcinoma             | 3                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Keratoacanthoma                              | 2                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Knuckle pads                                 | 0                                                                       | 0          | 0           | 3          | 3                 | 0                                                              | 0          |
|          | Large intestine benign neoplasm              | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Laryngeal neoplasm                           | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Laryngeal papilloma                          | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Leiomyoma                                    | 0                                                                       | 0          | 2           | 2          | 2                 | 0                                                              | 0          |
|          | Leiomyosarcoma                               | 0                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Leukaemia                                    | 11                                                                      | 16         | 0           | 0          | 16                | 0                                                              | 0          |
|          | Leukaemia in remission                       | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Leukaemia monocytic                          | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Leukaemia recurrent                          | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Leukaemic infiltration hepatic               | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Lip and/or oral cavity cancer                | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Lipoma                                       | 7                                                                       | 7          | 14          | 19         | 26                | 0                                                              | 0          |
|          | Lung adenocarcinoma                          | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Lung adenocarcinoma stage IV                 | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Lung cancer metastatic                       | 2                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Lung carcinoma cell type unspecified recurr  | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Lung carcinoma cell type unspecified stage   | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Lung neoplasm                                | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Lung neoplasm malignant                      | 14                                                                      | 19         | 0           | 0          | 19                | 0                                                              | 0          |
|          | Lymphatic system neoplasm                    | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Lymphocytic leukaemia                        | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Lymphoma                                     | 20                                                                      | 32         | 5           | 5          | 37                | 0                                                              | 0          |
|          | Lymphoproliferative disorder                 | 2                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Malignant ascites                            | 1                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Malignant melanoma                           | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Malignant melanoma stage IV                  | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Malignant neoplasm of unknown primary s      | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Malignant neoplasm progression               | 1                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Malignant pleural effusion                   | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Mantle cell lymphoma                         | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Marrow hyperplasia                           | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Melanocytic naevus                           | 0                                                                       | 0          | 8           | 12         | 12                | 0                                                              | 0          |
|          | Meningeal neoplasm                           | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Meningioma                                   | 4                                                                       | 7          | 0           | 0          | 7                 | 0                                                              | 0          |
|          | Meningioma benign                            | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Metastases to bone                           | 1                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |

|          |                                             | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|---------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                             | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                          | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Metastases to central nervous system        | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Metastases to liver                         | 4                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Metastases to lung                          | 3                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Metastases to lymph nodes                   | 6                                                                       | 7          | 0           | 0          | 7                 | 0                                                              | 0          |
|          | Metastases to meninges                      | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Metastases to oesophagus                    | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Metastases to pancreas                      | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Metastases to peritoneum                    | 2                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Metastases to reproductive organ            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Metastases to spine                         | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Metastases to spleen                        | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Metastases to trachea                       | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Metastasis                                  | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Metastatic carcinoid tumour                 | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Metastatic lymphoma                         | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Metastatic neoplasm                         | 8                                                                       | 12         | 0           | 0          | 12                | 0                                                              | 0          |
|          | Metastatic squamous cell carcinoma          | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Minimal residual disease                    | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Monoclonal gammopathy                       | 1                                                                       | 2          | 0           | 1          | 3                 | 0                                                              | 0          |
|          | Myelodysplastic syndrome                    | 5                                                                       | 8          | 0           | 0          | 8                 | 0                                                              | 0          |
|          | Myeloid leukaemia                           | 2                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Myeloproliferative neoplasm                 | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Myxofibrosarcoma                            | 0                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Neoplasm                                    | 9                                                                       | 11         | 10          | 18         | 29                | 0                                                              | 0          |
|          | Neoplasm malignant                          | 29                                                                      | 40         | 1           | 1          | 41                | 0                                                              | 0          |
|          | Neoplasm progression                        | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Neoplasm skin                               | 0                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Neuroendocrine carcinoma                    | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Neuroendocrine tumour                       | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Neuroma                                     | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Nodular fasciitis                           | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Non-Hodgkin's lymphoma                      | 7                                                                       | 7          | 0           | 0          | 7                 | 0                                                              | 0          |
|          | Non-small cell lung cancer stage IV         | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Oesophageal adenocarcinoma                  | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Oesophageal carcinoma                       | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Osteochondroma                              | 0                                                                       | 0          | 2           | 2          | 2                 | 0                                                              | 0          |
|          | Osteoma                                     | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Ovarian cancer                              | 4                                                                       | 6          | 0           | 0          | 6                 | 0                                                              | 0          |
|          | Ovarian cancer metastatic                   | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Ovarian neoplasm                            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Pancreatic carcinoma                        | 5                                                                       | 9          | 0           | 0          | 9                 | 0                                                              | 0          |
|          | Pancreatic carcinoma metastatic             | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Pancreatic neoplasm                         | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Papilloma                                   | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Paraproteinaemia                            | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Peripheral T-cell lymphoma unspecified      | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Phaeochromocytoma                           | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Philadelphia positive acute lymphocytic leu | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Pituitary tumour benign                     | 0                                                                       | 2          | 0           | 1          | 3                 | 0                                                              | 0          |

|                          |                                           | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|--------------------------|-------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|                          |                                           | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM                 | PT                                        | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|                          | Plasma cell myeloma                       | 13                                                                      | 17         | 0           | 0          | 17                | 0                                                              | 0          |
|                          | Plasma cell myeloma recurrent             | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                          | Pleomorphic adenoma                       | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                          | Polycythaemia vera                        | 3                                                                       | 6          | 0           | 0          | 6                 | 0                                                              | 0          |
|                          | Primary mediastinal large B-cell lymphoma | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                          | Prostate cancer                           | 6                                                                       | 8          | 1           | 1          | 9                 | 0                                                              | 0          |
|                          | Prostate cancer metastatic                | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                          | Prostate cancer stage IV                  | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                          | Pyogenic granuloma                        | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|                          | Rectal cancer metastatic                  | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                          | Renal cancer                              | 3                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|                          | Renal neoplasm                            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                          | Retroperitoneal cancer                    | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                          | Sarcoma                                   | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                          | Seborrhoeic keratosis                     | 1                                                                       | 1          | 0           | 4          | 5                 | 0                                                              | 0          |
|                          | Seminoma                                  | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                          | Skin cancer                               | 2                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|                          | Skin papilloma                            | 5                                                                       | 7          | 5           | 18         | 25                | 0                                                              | 0          |
|                          | Small cell carcinoma                      | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                          | Small cell lung cancer metastatic         | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                          | Small intestine adenocarcinoma            | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                          | Spinal cord lipoma                        | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                          | Squamous cell carcinoma                   | 2                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|                          | Squamous cell carcinoma of lung           | 0                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                          | Squamous cell carcinoma of skin           | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|                          | Systemic mastocytosis                     | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|                          | T-cell lymphoma                           | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                          | Testis cancer                             | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|                          | Thyroid cancer                            | 7                                                                       | 8          | 0           | 0          | 8                 | 0                                                              | 0          |
|                          | Thyroid cancer metastatic                 | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                          | Thyroid neoplasm                          | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|                          | Tonsil cancer                             | 0                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|                          | Tracheal neoplasm                         | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                          | Transitional cell carcinoma               | 2                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|                          | Transitional cell carcinoma metastatic    | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                          | Triple negative breast cancer             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                          | Tubular breast carcinoma                  | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                          | Tumour haemorrhage                        | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                          | Tumour pain                               | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                          | Uterine cancer                            | 0                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                          | Uterine leiomyoma                         | 4                                                                       | 6          | 8           | 14         | 20                | 0                                                              | 0          |
|                          | Vascular neoplasm                         | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
| Nervous system disorders | *** SOC TOTAL ***                         | 32410                                                                   | 54273      | 61667       | 162694     | 216967            | 4                                                              | 4          |
|                          | Accessory nerve disorder                  | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|                          | Acquired epileptic aphasia                | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                          | Action tremor                             | 0                                                                       | 3          | 0           | 1          | 4                 | 0                                                              | 0          |
|                          | Acute disseminated encephalomyelitis      | 25                                                                      | 30         | 2           | 2          | 32                | 0                                                              | 0          |
|                          | Acute motor axonal neuropathy             | 3                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|                          | Acute motor-sensory axonal neuropathy     | 3                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |



|          |                                         | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|-----------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                         | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                      | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Acute polyneuropathy                    | 7                                                                       | 9          | 0           | 0          | 9                 | 0                                                              | 0          |
|          | Ageusia                                 | 166                                                                     | 220        | 836         | 2031       | 2251              | 0                                                              | 0          |
|          | Agitation neonatal                      | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Agnosia                                 | 0                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Agraphia                                | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Akathisia                               | 2                                                                       | 3          | 1           | 5          | 8                 | 0                                                              | 0          |
|          | Akinesia                                | 1                                                                       | 9          | 0           | 0          | 9                 | 0                                                              | 0          |
|          | Allodynia                               | 4                                                                       | 7          | 2           | 28         | 35                | 0                                                              | 0          |
|          | Altered state of consciousness          | 137                                                                     | 208        | 8           | 12         | 220               | 0                                                              | 0          |
|          | Amnesia                                 | 134                                                                     | 220        | 144         | 386        | 606               | 0                                                              | 0          |
|          | Amnesic disorder                        | 5                                                                       | 9          | 0           | 0          | 9                 | 0                                                              | 0          |
|          | Amputation stump pain                   | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Amyotrophic lateral sclerosis           | 10                                                                      | 11         | 0           | 0          | 11                | 0                                                              | 0          |
|          | Anaesthesia                             | 6                                                                       | 6          | 13          | 21         | 27                | 0                                                              | 0          |
|          | Anosmia                                 | 121                                                                     | 153        | 698         | 1483       | 1636              | 0                                                              | 0          |
|          | Anosognosia                             | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Anterior spinal artery syndrome         | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Anterograde amnesia                     | 1                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Apallic syndrome                        | 4                                                                       | 7          | 0           | 0          | 7                 | 0                                                              | 0          |
|          | Aphasia                                 | 172                                                                     | 407        | 103         | 344        | 751               | 0                                                              | 0          |
|          | Apraxia                                 | 5                                                                       | 12         | 2           | 4          | 16                | 0                                                              | 0          |
|          | Arachnoid cyst                          | 1                                                                       | 4          | 0           | 2          | 6                 | 0                                                              | 0          |
|          | Arachnoid web                           | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Arachnoiditis                           | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Areflexia                               | 9                                                                       | 20         | 0           | 5          | 25                | 0                                                              | 0          |
|          | Asterixis                               | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Ataxia                                  | 28                                                                      | 52         | 7           | 39         | 91                | 0                                                              | 0          |
|          | Atonic seizures                         | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|          | Auditory nerve disorder                 | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Aura                                    | 5                                                                       | 5          | 8           | 36         | 41                | 0                                                              | 0          |
|          | Autoimmune demyelinating disease        | 2                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Autoimmune encephalopathy               | 1                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Autoimmune neuropathy                   | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Autonomic nervous system imbalance      | 9                                                                       | 14         | 10          | 20         | 34                | 0                                                              | 0          |
|          | Autonomic neuropathy                    | 6                                                                       | 8          | 0           | 1          | 9                 | 0                                                              | 0          |
|          | Axonal and demyelinating polyneuropathy | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Axonal neuropathy                       | 1                                                                       | 2          | 1           | 1          | 3                 | 0                                                              | 0          |
|          | Balance disorder                        | 250                                                                     | 410        | 351         | 1209       | 1619              | 0                                                              | 0          |
|          | Ballismus                               | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|          | Band sensation                          | 3                                                                       | 4          | 1           | 3          | 7                 | 0                                                              | 0          |
|          | Basal ganglia haemorrhage               | 3                                                                       | 8          | 0           | 0          | 8                 | 0                                                              | 0          |
|          | Basal ganglia infarction                | 2                                                                       | 6          | 0           | 0          | 6                 | 0                                                              | 0          |
|          | Basal ganglia stroke                    | 3                                                                       | 16         | 0           | 0          | 16                | 0                                                              | 0          |
|          | Basilar artery aneurysm                 | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Basilar artery occlusion                | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Basilar artery stenosis                 | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Basilar artery thrombosis               | 5                                                                       | 8          | 0           | 0          | 8                 | 0                                                              | 0          |
|          | Basilar migraine                        | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Bell's palsy                            | 504                                                                     | 1536       | 87          | 123        | 1659              | 0                                                              | 0          |

|          |                                              | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|----------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                              | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                           | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Benign enlargement of the subarachnoid space | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Bickerstaff's encephalitis                   | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Blood brain barrier defect                   | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Brachial plexopathy                          | 5                                                                       | 8          | 4           | 4          | 12                | 0                                                              | 0          |
|          | Bradykinesia                                 | 8                                                                       | 11         | 23          | 58         | 69                | 0                                                              | 0          |
|          | Brain compression                            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Brain hypoxia                                | 2                                                                       | 6          | 0           | 0          | 6                 | 0                                                              | 0          |
|          | Brain injury                                 | 16                                                                      | 33         | 0           | 0          | 33                | 0                                                              | 0          |
|          | Brain oedema                                 | 37                                                                      | 65         | 1           | 4          | 69                | 0                                                              | 0          |
|          | Brain stem embolism                          | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Brain stem haemorrhage                       | 4                                                                       | 8          | 0           | 0          | 8                 | 0                                                              | 0          |
|          | Brain stem infarction                        | 7                                                                       | 22         | 0           | 0          | 22                | 0                                                              | 0          |
|          | Brain stem stroke                            | 8                                                                       | 14         | 0           | 0          | 14                | 0                                                              | 0          |
|          | Brain stem syndrome                          | 4                                                                       | 6          | 0           | 0          | 6                 | 0                                                              | 0          |
|          | Brain stem thrombosis                        | 3                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Brown-Sequard syndrome                       | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Brudzinski's sign                            | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Bulbar palsy                                 | 2                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Burning feet syndrome                        | 5                                                                       | 5          | 1           | 3          | 8                 | 0                                                              | 0          |
|          | Burning sensation                            | 217                                                                     | 292        | 596         | 2335       | 2627              | 0                                                              | 0          |
|          | Burning sensation mucosal                    | 0                                                                       | 0          | 1           | 4          | 4                 | 0                                                              | 0          |
|          | Carotid arteriosclerosis                     | 1                                                                       | 7          | 1           | 1          | 8                 | 0                                                              | 0          |
|          | Carotid artery aneurysm                      | 0                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Carotid artery disease                       | 3                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Carotid artery dissection                    | 7                                                                       | 11         | 0           | 0          | 11                | 0                                                              | 0          |
|          | Carotid artery occlusion                     | 13                                                                      | 25         | 0           | 0          | 25                | 0                                                              | 0          |
|          | Carotid artery stenosis                      | 11                                                                      | 24         | 0           | 0          | 24                | 0                                                              | 0          |
|          | Carotid artery thrombosis                    | 12                                                                      | 15         | 0           | 0          | 15                | 0                                                              | 0          |
|          | Carpal tunnel syndrome                       | 8                                                                       | 13         | 14          | 33         | 46                | 0                                                              | 0          |
|          | Cataplexy                                    | 5                                                                       | 8          | 0           | 0          | 8                 | 0                                                              | 0          |
|          | Cauda equina syndrome                        | 5                                                                       | 6          | 0           | 0          | 6                 | 0                                                              | 0          |
|          | Central nervous system haemorrhage           | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Central nervous system inflammation          | 4                                                                       | 6          | 0           | 0          | 6                 | 0                                                              | 0          |
|          | Central nervous system lesion                | 17                                                                      | 29         | 7           | 8          | 37                | 0                                                              | 0          |
|          | Central nervous system vasculitis            | 2                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Central pain syndrome                        | 3                                                                       | 3          | 1           | 5          | 8                 | 0                                                              | 0          |
|          | Cerebellar artery occlusion                  | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Cerebellar artery thrombosis                 | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Cerebellar ataxia                            | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Cerebellar atrophy                           | 0                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Cerebellar haematoma                         | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Cerebellar haemorrhage                       | 3                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Cerebellar infarction                        | 12                                                                      | 21         | 0           | 0          | 21                | 0                                                              | 0          |
|          | Cerebellar stroke                            | 16                                                                      | 37         | 1           | 1          | 38                | 0                                                              | 0          |
|          | Cerebellar syndrome                          | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Cerebral amyloid angiopathy                  | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Cerebral aneurysm perforation                | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Cerebral arteriosclerosis                    | 2                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Cerebral artery embolism                     | 4                                                                       | 9          | 0           | 0          | 9                 | 0                                                              | 0          |

|          |                                           | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|-------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                           | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                        | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Cerebral artery occlusion                 | 10                                                                      | 28         | 0           | 0          | 28                | 0                                                              | 0          |
|          | Cerebral artery perforation               | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Cerebral artery stenosis                  | 8                                                                       | 14         | 0           | 0          | 14                | 0                                                              | 0          |
|          | Cerebral artery thrombosis                | 2                                                                       | 7          | 0           | 0          | 7                 | 0                                                              | 0          |
|          | Cerebral ataxia                           | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Cerebral atrophy                          | 18                                                                      | 28         | 0           | 0          | 28                | 0                                                              | 0          |
|          | Cerebral calcification                    | 1                                                                       | 2          | 1           | 3          | 5                 | 0                                                              | 0          |
|          | Cerebral congestion                       | 1                                                                       | 2          | 1           | 6          | 8                 | 0                                                              | 0          |
|          | Cerebral cyst                             | 1                                                                       | 2          | 0           | 2          | 4                 | 0                                                              | 0          |
|          | Cerebral disorder                         | 7                                                                       | 12         | 10          | 25         | 37                | 0                                                              | 0          |
|          | Cerebral haematoma                        | 9                                                                       | 12         | 1           | 1          | 13                | 0                                                              | 0          |
|          | Cerebral haemorrhage                      | 126                                                                     | 251        | 0           | 1          | 252               | 0                                                              | 0          |
|          | Cerebral haemorrhage foetal               | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Cerebral haemorrhage neonatal             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Cerebral hypoperfusion                    | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Cerebral infarction                       | 113                                                                     | 218        | 2           | 3          | 221               | 0                                                              | 0          |
|          | Cerebral ischaemia                        | 19                                                                      | 41         | 0           | 0          | 41                | 0                                                              | 0          |
|          | Cerebral mass effect                      | 6                                                                       | 18         | 0           | 0          | 18                | 0                                                              | 0          |
|          | Cerebral microangiopathy                  | 0                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Cerebral microembolism                    | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Cerebral microhaemorrhage                 | 3                                                                       | 3          | 1           | 1          | 4                 | 0                                                              | 0          |
|          | Cerebral microinfarction                  | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Cerebral reperfusion injury               | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Cerebral small vessel ischaemic disease   | 24                                                                      | 50         | 2           | 2          | 52                | 0                                                              | 0          |
|          | Cerebral thrombosis                       | 60                                                                      | 106        | 0           | 0          | 106               | 0                                                              | 0          |
|          | Cerebral vascular occlusion               | 4                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Cerebral vasoconstriction                 | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Cerebral venous sinus thrombosis          | 63                                                                      | 113        | 1           | 1          | 114               | 0                                                              | 0          |
|          | Cerebral venous thrombosis                | 26                                                                      | 38         | 0           | 0          | 38                | 0                                                              | 0          |
|          | Cerebral ventricle dilatation             | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Cerebral ventricular rupture              | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Cerebro sclerosis                         | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Cerebrospinal fluid circulation disorder  | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Cerebrospinal fluid leakage               | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Cerebrovascular accident                  | 703                                                                     | 1559       | 14          | 16         | 1575              | 0                                                              | 0          |
|          | Cerebrovascular disorder                  | 6                                                                       | 8          | 0           | 0          | 8                 | 0                                                              | 0          |
|          | Cervical radiculopathy                    | 2                                                                       | 5          | 3           | 7          | 12                | 0                                                              | 0          |
|          | Cervicobrachial syndrome                  | 3                                                                       | 4          | 5           | 7          | 11                | 0                                                              | 0          |
|          | Cervicogenic headache                     | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|          | Change in seizure presentation            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Chorea                                    | 0                                                                       | 2          | 0           | 2          | 4                 | 0                                                              | 0          |
|          | Choreoathetosis                           | 0                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Chronic inflammatory demyelinating polyra | 17                                                                      | 23         | 0           | 1          | 24                | 0                                                              | 0          |
|          | Circadian rhythm sleep disorder           | 0                                                                       | 0          | 1           | 5          | 5                 | 0                                                              | 0          |
|          | Clonic convulsion                         | 10                                                                      | 11         | 0           | 0          | 11                | 0                                                              | 0          |
|          | Clonus                                    | 3                                                                       | 4          | 3           | 7          | 11                | 0                                                              | 0          |
|          | Clumsiness                                | 10                                                                      | 13         | 3           | 15         | 28                | 0                                                              | 0          |
|          | Cluster headache                          | 48                                                                      | 54         | 24          | 57         | 111               | 0                                                              | 0          |
|          | Cognitive disorder                        | 84                                                                      | 134        | 52          | 195        | 329               | 0                                                              | 0          |

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|----------|----------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                  | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                               | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Cognitive linguistic deficit     | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Cogwheel rigidity                | 0                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Cold dysaesthesia                | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Cold-stimulus headache           | 10                                                                      | 11         | 2           | 12         | 23                | 0                                                              | 0          |
|          | Colloid brain cyst               | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Coma                             | 37                                                                      | 64         | 2           | 2          | 66                | 0                                                              | 0          |
|          | Complex regional pain syndrome   | 11                                                                      | 13         | 5           | 11         | 24                | 0                                                              | 0          |
|          | Consciousness fluctuating        | 16                                                                      | 36         | 1           | 2          | 38                | 0                                                              | 0          |
|          | Conus medullaris syndrome        | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Convulsions local                | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Coordination abnormal            | 40                                                                      | 63         | 41          | 105        | 168               | 0                                                              | 0          |
|          | Cortical laminar necrosis        | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Cramp-fasciculation syndrome     | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Cranial nerve disorder           | 9                                                                       | 14         | 4           | 13         | 27                | 0                                                              | 0          |
|          | Cranial nerve palsies multiple   | 2                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Cranial nerve paralysis          | 1                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Cubital tunnel syndrome          | 0                                                                       | 0          | 2           | 4          | 4                 | 0                                                              | 0          |
|          | Cytotoxic oedema                 | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Decerebrate posture              | 0                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Decreased vibratory sense        | 0                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Delayed sleep phase              | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Dementia                         | 44                                                                      | 92         | 3           | 8          | 100               | 0                                                              | 0          |
|          | Dementia Alzheimer's type        | 10                                                                      | 16         | 1           | 1          | 17                | 0                                                              | 0          |
|          | Demyelinating polyneuropathy     | 12                                                                      | 20         | 0           | 0          | 20                | 0                                                              | 0          |
|          | Demyelination                    | 20                                                                      | 33         | 1           | 1          | 34                | 0                                                              | 0          |
|          | Depressed level of consciousness | 171                                                                     | 306        | 11          | 18         | 324               | 0                                                              | 0          |
|          | Diabetic coma                    | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Diabetic hyperosmolar coma       | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Diabetic neuropathy              | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Diplegia                         | 29                                                                      | 56         | 4           | 6          | 62                | 0                                                              | 0          |
|          | Disturbance in attention         | 176                                                                     | 236        | 487         | 994        | 1230              | 0                                                              | 0          |
|          | Dizziness                        | 3427                                                                    | 4727       | 8938        | 26792      | 31519             | 1                                                              | 1          |
|          | Dizziness exertional             | 14                                                                      | 15         | 9           | 18         | 33                | 0                                                              | 0          |
|          | Dizziness postural               | 159                                                                     | 189        | 105         | 285        | 474               | 0                                                              | 0          |
|          | Dreamy state                     | 0                                                                       | 1          | 1           | 8          | 9                 | 0                                                              | 0          |
|          | Drizzling                        | 11                                                                      | 22         | 10          | 61         | 83                | 0                                                              | 0          |
|          | Drop attacks                     | 5                                                                       | 7          | 0           | 0          | 7                 | 0                                                              | 0          |
|          | Drug withdrawal headache         | 1                                                                       | 2          | 1           | 1          | 3                 | 0                                                              | 0          |
|          | Dysaesthesia                     | 31                                                                      | 38         | 134         | 159        | 197               | 0                                                              | 0          |
|          | Dysarthria                       | 187                                                                     | 357        | 72          | 324        | 681               | 0                                                              | 0          |
|          | Dyscalculia                      | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|          | Dysgeusia                        | 125                                                                     | 179        | 424         | 1698       | 1877              | 0                                                              | 0          |
|          | Dysgraphia                       | 12                                                                      | 22         | 8           | 16         | 38                | 0                                                              | 0          |
|          | Dyskinesia                       | 53                                                                      | 101        | 100         | 329        | 430               | 0                                                              | 0          |
|          | Dyslalia                         | 3                                                                       | 3          | 1           | 2          | 5                 | 0                                                              | 0          |
|          | Dyslexia                         | 1                                                                       | 2          | 2           | 5          | 7                 | 0                                                              | 0          |
|          | Dysmetria                        | 1                                                                       | 2          | 2           | 2          | 4                 | 0                                                              | 0          |
|          | Dyspraxia                        | 0                                                                       | 1          | 1           | 3          | 4                 | 0                                                              | 0          |
|          | Dysstasia                        | 135                                                                     | 246        | 191         | 723        | 969               | 0                                                              | 0          |

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|----------|-------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                     | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                  | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Dystonia                            | 8                                                                       | 24         | 0           | 2          | 26                | 0                                                              | 0          |
|          | Dystonic tremor                     | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Electric shock sensation            | 37                                                                      | 49         | 56          | 144        | 193               | 0                                                              | 0          |
|          | Embolic cerebellar infarction       | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Embolic cerebral infarction         | 6                                                                       | 10         | 0           | 0          | 10                | 0                                                              | 0          |
|          | Embolic stroke                      | 16                                                                      | 31         | 0           | 0          | 31                | 0                                                              | 0          |
|          | Encephalitis allergic               | 0                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Encephalitis autoimmune             | 6                                                                       | 10         | 0           | 0          | 10                | 0                                                              | 0          |
|          | Encephalitis post immunisation      | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Encephalomalacia                    | 3                                                                       | 5          | 0           | 1          | 6                 | 0                                                              | 0          |
|          | Encephalopathy                      | 83                                                                      | 151        | 0           | 1          | 152               | 0                                                              | 0          |
|          | Epilepsy                            | 153                                                                     | 226        | 12          | 13         | 239               | 1                                                              | 1          |
|          | Epileptic aura                      | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Essential tremor                    | 4                                                                       | 7          | 0           | 6          | 13                | 0                                                              | 0          |
|          | Exaggerated startle response        | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Exertional headache                 | 1                                                                       | 2          | 3           | 5          | 7                 | 0                                                              | 0          |
|          | Extensor plantar response           | 2                                                                       | 3          | 0           | 1          | 4                 | 0                                                              | 0          |
|          | External compression headache       | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|          | Extrapyramidal disorder             | 1                                                                       | 2          | 2           | 4          | 6                 | 0                                                              | 0          |
|          | Facial nerve disorder               | 3                                                                       | 5          | 4           | 9          | 14                | 0                                                              | 0          |
|          | Facial paralysis                    | 622                                                                     | 1276       | 68          | 94         | 1370              | 0                                                              | 0          |
|          | Facial paresis                      | 86                                                                      | 145        | 67          | 142        | 287               | 0                                                              | 0          |
|          | Facial spasm                        | 9                                                                       | 12         | 15          | 30         | 42                | 0                                                              | 0          |
|          | Febrile convulsion                  | 15                                                                      | 18         | 15          | 20         | 38                | 0                                                              | 0          |
|          | Femoral nerve palsy                 | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Fine motor delay                    | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Fine motor skill dysfunction        | 18                                                                      | 29         | 9           | 25         | 54                | 0                                                              | 0          |
|          | Focal dyscognitive seizures         | 1                                                                       | 6          | 0           | 0          | 6                 | 0                                                              | 0          |
|          | Foetal cerebrovascular disorder     | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Foetal movement disorder            | 1                                                                       | 2          | 2           | 2          | 4                 | 0                                                              | 0          |
|          | Formication                         | 26                                                                      | 31         | 57          | 151        | 182               | 0                                                              | 0          |
|          | Freezing phenomenon                 | 11                                                                      | 11         | 12          | 35         | 46                | 0                                                              | 0          |
|          | Fumbling                            | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Gait spastic                        | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|          | Generalised onset non-motor seizure | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Generalised tonic-clonic seizure    | 85                                                                      | 196        | 10          | 10         | 206               | 0                                                              | 0          |
|          | Glossopharyngeal nerve disorder     | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Glossopharyngeal neuralgia          | 0                                                                       | 1          | 1           | 3          | 4                 | 0                                                              | 0          |
|          | Grimacing                           | 2                                                                       | 2          | 0           | 1          | 3                 | 0                                                              | 0          |
|          | Gross motor delay                   | 0                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Guillain-Barre syndrome             | 226                                                                     | 384        | 4           | 4          | 388               | 0                                                              | 0          |
|          | Gulf war syndrome                   | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Haemorrhage intracranial            | 13                                                                      | 28         | 0           | 1          | 29                | 0                                                              | 0          |
|          | Haemorrhagic cerebral infarction    | 2                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Haemorrhagic stroke                 | 30                                                                      | 61         | 0           | 0          | 61                | 0                                                              | 0          |
|          | Haemorrhagic transformation stroke  | 7                                                                       | 12         | 0           | 0          | 12                | 0                                                              | 0          |
|          | Hand-arm vibration syndrome         | 0                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Hand-eye coordination impaired      | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Hashimoto's encephalopathy          | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |

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|          |                                       | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                    | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Head discomfort                       | 99                                                                      | 142        | 379         | 1105       | 1247              | 0                                                              | 0          |
|          | Head titubation                       | 5                                                                       | 8          | 8           | 26         | 34                | 0                                                              | 0          |
|          | Headache                              | 8267                                                                    | 10283      | 32148       | 79051      | 89334             | 2                                                              | 2          |
|          | Hemianaesthesia                       | 27                                                                      | 35         | 2           | 3          | 38                | 0                                                              | 0          |
|          | Hemianopia                            | 4                                                                       | 10         | 0           | 0          | 10                | 0                                                              | 0          |
|          | Hemianopia homonymous                 | 3                                                                       | 7          | 0           | 1          | 8                 | 0                                                              | 0          |
|          | Hemiasomatognosia                     | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Hemiataxia                            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Hemidysaesthesia                      | 3                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Hemiparaesthesia                      | 26                                                                      | 46         | 8           | 9          | 55                | 0                                                              | 0          |
|          | Hemiparesis                           | 187                                                                     | 407        | 6           | 10         | 417               | 0                                                              | 0          |
|          | Hemiplegia                            | 91                                                                      | 175        | 3           | 5          | 180               | 0                                                              | 0          |
|          | Hemiplegic migraine                   | 7                                                                       | 9          | 4           | 7          | 16                | 0                                                              | 0          |
|          | Hepatic encephalopathy                | 5                                                                       | 9          | 0           | 0          | 9                 | 0                                                              | 0          |
|          | Hoffmann's sign                       | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Horner's syndrome                     | 3                                                                       | 6          | 1           | 1          | 7                 | 0                                                              | 0          |
|          | Hydrocephalus                         | 11                                                                      | 13         | 0           | 0          | 13                | 0                                                              | 0          |
|          | Hyperaesthesia                        | 46                                                                      | 62         | 142         | 289        | 351               | 0                                                              | 0          |
|          | Hyperammonaemic encephalopathy        | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Hyperintensity in brain deep nuclei   | 2                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Hyperkinesia                          | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Hyperpathia                           | 0                                                                       | 0          | 1           | 3          | 3                 | 0                                                              | 0          |
|          | Hyperreflexia                         | 2                                                                       | 6          | 2           | 3          | 9                 | 0                                                              | 0          |
|          | Hypersomnia                           | 80                                                                      | 110        | 332         | 1158       | 1268              | 0                                                              | 0          |
|          | Hypertensive encephalopathy           | 0                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Hypertonia                            | 4                                                                       | 8          | 7           | 14         | 22                | 0                                                              | 0          |
|          | Hypoaesthesia                         | 1165                                                                    | 1749       | 2443        | 7009       | 8758              | 0                                                              | 0          |
|          | Hypogeusia                            | 11                                                                      | 15         | 27          | 58         | 73                | 0                                                              | 0          |
|          | Hypoglossal nerve disorder            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Hypoglossal nerve paralysis           | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Hypoglycaemic coma                    | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Hypoglycaemic seizure                 | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Hypoglycaemic unconsciousness         | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Hypokinesia                           | 33                                                                      | 69         | 134         | 512        | 581               | 0                                                              | 0          |
|          | Hyporeflexia                          | 10                                                                      | 16         | 5           | 8          | 24                | 0                                                              | 0          |
|          | Hyporesponsive to stimuli             | 9                                                                       | 28         | 1           | 8          | 36                | 0                                                              | 0          |
|          | Hyposmia                              | 7                                                                       | 10         | 27          | 49         | 59                | 0                                                              | 0          |
|          | Hypotonia                             | 41                                                                      | 55         | 129         | 169        | 224               | 0                                                              | 0          |
|          | Hypotonic-hyporesponsive episode      | 1                                                                       | 5          | 1           | 1          | 6                 | 0                                                              | 0          |
|          | Hypoxic-ischaemic encephalopathy      | 11                                                                      | 14         | 0           | 0          | 14                | 0                                                              | 0          |
|          | Illrd nerve paralysis                 | 7                                                                       | 23         | 0           | 0          | 23                | 0                                                              | 0          |
|          | Illrd nerve paresis                   | 2                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | IVth nerve paralysis                  | 1                                                                       | 8          | 0           | 0          | 8                 | 0                                                              | 0          |
|          | IVth nerve paresis                    | 0                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Idiopathic intracranial hypertension  | 7                                                                       | 8          | 0           | 0          | 8                 | 0                                                              | 0          |
|          | Immune-mediated encephalitis          | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Immune-mediated neurological disorder | 0                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Immune-mediated neuropathy            | 2                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Inability to crawl                    | 1                                                                       | 1          | 0           | 3          | 4                 | 0                                                              | 0          |

|          |                                       | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|---------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                       | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                    | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Incoherent                            | 15                                                                      | 37         | 15          | 86         | 123               | 0                                                              | 0          |
|          | Infant irritability                   | 2                                                                       | 2          | 0           | 1          | 3                 | 0                                                              | 0          |
|          | Intellectual disability               | 3                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Intention tremor                      | 3                                                                       | 4          | 1           | 4          | 8                 | 0                                                              | 0          |
|          | Intercostal neuralgia                 | 2                                                                       | 2          | 1           | 1          | 3                 | 0                                                              | 0          |
|          | Internal capsule infarction           | 2                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Intracranial aneurysm                 | 16                                                                      | 34         | 0           | 0          | 34                | 0                                                              | 0          |
|          | Intracranial haematoma                | 2                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Intracranial hypotension              | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Intracranial mass                     | 1                                                                       | 5          | 0           | 1          | 6                 | 0                                                              | 0          |
|          | Intracranial pressure increased       | 10                                                                      | 24         | 0           | 0          | 24                | 0                                                              | 0          |
|          | Intraventricular haemorrhage          | 11                                                                      | 17         | 0           | 0          | 17                | 0                                                              | 0          |
|          | Intraventricular haemorrhage neonatal | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Irregular sleep phase                 | 1                                                                       | 1          | 2           | 3          | 4                 | 0                                                              | 0          |
|          | Irregular sleep wake rhythm disorder  | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|          | Ischaemic cerebral infarction         | 15                                                                      | 28         | 0           | 0          | 28                | 0                                                              | 0          |
|          | Ischaemic stroke                      | 171                                                                     | 309        | 1           | 1          | 310               | 0                                                              | 0          |
|          | Judgement impaired                    | 0                                                                       | 1          | 0           | 2          | 3                 | 0                                                              | 0          |
|          | Juvenile myoclonic epilepsy           | 0                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Lacunar infarction                    | 12                                                                      | 29         | 0           | 0          | 29                | 0                                                              | 0          |
|          | Lacunar stroke                        | 5                                                                       | 15         | 0           | 0          | 15                | 0                                                              | 0          |
|          | Language disorder                     | 17                                                                      | 21         | 20          | 22         | 43                | 0                                                              | 0          |
|          | Laryngeal tremor                      | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Lateral medullary syndrome            | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Lethargy                              | 423                                                                     | 626        | 348         | 2087       | 2713              | 0                                                              | 0          |
|          | Leukoencephalopathy                   | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Lhermitte's sign                      | 2                                                                       | 2          | 2           | 3          | 5                 | 0                                                              | 0          |
|          | Limbic encephalitis                   | 4                                                                       | 6          | 0           | 0          | 6                 | 0                                                              | 0          |
|          | Long thoracic nerve palsy             | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Loss of consciousness                 | 1341                                                                    | 3919       | 163         | 434        | 4353              | 0                                                              | 0          |
|          | Loss of proprioception                | 1                                                                       | 3          | 1           | 2          | 5                 | 0                                                              | 0          |
|          | Lumbar radiculopathy                  | 1                                                                       | 2          | 1           | 2          | 4                 | 0                                                              | 0          |
|          | Lumbosacral plexopathy                | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Lumbosacral radiculopathy             | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|          | Medication overuse headache           | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Memory impairment                     | 159                                                                     | 237        | 267         | 573        | 810               | 0                                                              | 0          |
|          | Meningeal disorder                    | 1                                                                       | 2          | 1           | 2          | 4                 | 0                                                              | 0          |
|          | Meningism                             | 4                                                                       | 10         | 8           | 9          | 19                | 0                                                              | 0          |
|          | Meningitis noninfective               | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Meningoradiculitis                    | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Meningorrhagia                        | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Mental impairment                     | 68                                                                      | 229        | 7           | 21         | 250               | 0                                                              | 0          |
|          | Meralgia paraesthetica                | 0                                                                       | 0          | 1           | 3          | 3                 | 0                                                              | 0          |
|          | Metabolic encephalopathy              | 27                                                                      | 44         | 0           | 0          | 44                | 0                                                              | 0          |
|          | Microvascular cranial nerve palsy     | 0                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Migraine                              | 766                                                                     | 935        | 943         | 2937       | 3872              | 0                                                              | 0          |
|          | Migraine with aura                    | 38                                                                      | 49         | 37          | 83         | 132               | 0                                                              | 0          |
|          | Migraine without aura                 | 3                                                                       | 3          | 1           | 3          | 6                 | 0                                                              | 0          |
|          | Migraine-triggered seizure            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |

|          |                                              | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|----------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                              | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                           | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Miller Fisher syndrome                       | 11                                                                      | 16         | 0           | 0          | 16                | 0                                                              | 0          |
|          | Mononeuritis                                 | 1                                                                       | 1          | 2           | 3          | 4                 | 0                                                              | 0          |
|          | Mononeuropathy                               | 3                                                                       | 3          | 0           | 1          | 4                 | 0                                                              | 0          |
|          | Mononeuropathy multiplex                     | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Monoparesis                                  | 25                                                                      | 35         | 20          | 32         | 67                | 0                                                              | 0          |
|          | Monoplegia                                   | 84                                                                      | 174        | 15          | 19         | 193               | 0                                                              | 0          |
|          | Morton's neuralgia                           | 0                                                                       | 0          | 2           | 2          | 2                 | 0                                                              | 0          |
|          | Motor dysfunction                            | 32                                                                      | 56         | 38          | 79         | 135               | 0                                                              | 0          |
|          | Motor neurone disease                        | 4                                                                       | 6          | 0           | 0          | 6                 | 0                                                              | 0          |
|          | Movement disorder                            | 90                                                                      | 138        | 139         | 489        | 627               | 0                                                              | 0          |
|          | Multifocal motor neuropathy                  | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Multiple sclerosis                           | 70                                                                      | 112        | 3           | 6          | 118               | 0                                                              | 0          |
|          | Multiple sclerosis pseudo relapse            | 2                                                                       | 2          | 0           | 2          | 4                 | 0                                                              | 0          |
|          | Multiple sclerosis relapse                   | 42                                                                      | 70         | 0           | 0          | 70                | 0                                                              | 0          |
|          | Muscle contractions involuntary              | 23                                                                      | 30         | 55          | 108        | 138               | 0                                                              | 0          |
|          | Muscle spasticity                            | 11                                                                      | 17         | 6           | 26         | 43                | 0                                                              | 0          |
|          | Muscle tension dysphonia                     | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Muscle tone disorder                         | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Myasthenia gravis                            | 50                                                                      | 84         | 3           | 4          | 88                | 0                                                              | 0          |
|          | Myasthenia gravis crisis                     | 2                                                                       | 5          | 1           | 1          | 6                 | 0                                                              | 0          |
|          | Myasthenic syndrome                          | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Myelin oligodendrocyte glycoprotein antibody | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Myelitis transverse                          | 44                                                                      | 94         | 1           | 1          | 95                | 0                                                              | 0          |
|          | Myelomalacia                                 | 1                                                                       | 2          | 0           | 1          | 3                 | 0                                                              | 0          |
|          | Myelopathy                                   | 5                                                                       | 7          | 0           | 0          | 7                 | 0                                                              | 0          |
|          | Myoclonic epilepsy                           | 3                                                                       | 7          | 1           | 1          | 8                 | 0                                                              | 0          |
|          | Myoclonus                                    | 19                                                                      | 28         | 21          | 38         | 66                | 0                                                              | 0          |
|          | Myotonia                                     | 0                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Myxoedema coma                               | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Narcolepsy                                   | 12                                                                      | 19         | 0           | 0          | 19                | 0                                                              | 0          |
|          | Nerve compression                            | 7                                                                       | 17         | 17          | 50         | 67                | 0                                                              | 0          |
|          | Nerve degeneration                           | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Nervous system disorder                      | 54                                                                      | 74         | 41          | 79         | 153               | 0                                                              | 0          |
|          | Neuralgia                                    | 219                                                                     | 265        | 344         | 785        | 1050              | 0                                                              | 0          |
|          | Neuralgic amyotrophy                         | 50                                                                      | 61         | 8           | 32         | 93                | 0                                                              | 0          |
|          | Neuritis                                     | 8                                                                       | 11         | 18          | 34         | 45                | 0                                                              | 0          |
|          | Neurodegenerative disorder                   | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Neuroleptic malignant syndrome               | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Neurologic neglect syndrome                  | 2                                                                       | 7          | 1           | 1          | 8                 | 0                                                              | 0          |
|          | Neurological decompensation                  | 5                                                                       | 8          | 1           | 1          | 9                 | 0                                                              | 0          |
|          | Neurological symptom                         | 87                                                                      | 168        | 37          | 95         | 263               | 0                                                              | 0          |
|          | Neuromuscular blockade                       | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Neuromuscular pain                           | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|          | Neuromyelitis optica spectrum disorder       | 7                                                                       | 12         | 0           | 0          | 12                | 0                                                              | 0          |
|          | Neuromyopathy                                | 2                                                                       | 6          | 0           | 1          | 7                 | 0                                                              | 0          |
|          | Neuropathy peripheral                        | 239                                                                     | 455        | 27          | 48         | 503               | 0                                                              | 0          |
|          | Neurotoxicity                                | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | New daily persistent headache                | 7                                                                       | 7          | 13          | 16         | 23                | 0                                                              | 0          |
|          | Non-24-hour sleep-wake disorder              | 2                                                                       | 2          | 0           | 1          | 3                 | 0                                                              | 0          |



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|----------|------------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                                | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                             | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Noninfectious myelitis                         | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Noninfective encephalitis                      | 9                                                                       | 11         | 1           | 1          | 12                | 0                                                              | 0          |
|          | Normal pressure hydrocephalus                  | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Numb chin syndrome                             | 0                                                                       | 7          | 0           | 0          | 7                 | 0                                                              | 0          |
|          | Nystagmus                                      | 16                                                                      | 29         | 11          | 35         | 64                | 0                                                              | 0          |
|          | Occipital neuralgia                            | 4                                                                       | 7          | 6           | 17         | 24                | 0                                                              | 0          |
|          | Olfactory nerve disorder                       | 2                                                                       | 2          | 7           | 7          | 9                 | 0                                                              | 0          |
|          | On and off phenomenon                          | 0                                                                       | 0          | 1           | 5          | 5                 | 0                                                              | 0          |
|          | Ophthalmic migraine                            | 5                                                                       | 11         | 18          | 35         | 46                | 0                                                              | 0          |
|          | Opisthotonus                                   | 0                                                                       | 1          | 0           | 2          | 3                 | 0                                                              | 0          |
|          | Optic neuritis                                 | 52                                                                      | 80         | 1           | 1          | 81                | 0                                                              | 0          |
|          | Optic perineuritis                             | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Oromandibular dystonia                         | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Orthostatic intolerance                        | 5                                                                       | 6          | 9           | 11         | 17                | 0                                                              | 0          |
|          | Osmotic demyelination syndrome                 | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Pachymeningitis                                | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Paraesthesia                                   | 1304                                                                    | 1770       | 3334        | 8831       | 10601             | 0                                                              | 0          |
|          | Paraesthesia mucosal                           | 0                                                                       | 0          | 2           | 3          | 3                 | 0                                                              | 0          |
|          | Paralysis                                      | 195                                                                     | 340        | 18          | 28         | 368               | 0                                                              | 0          |
|          | Paralysis recurrent laryngeal nerve            | 2                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Paraparesis                                    | 7                                                                       | 9          | 0           | 2          | 11                | 0                                                              | 0          |
|          | Paraplegia                                     | 6                                                                       | 14         | 0           | 0          | 14                | 0                                                              | 0          |
|          | Paresis                                        | 18                                                                      | 21         | 17          | 22         | 43                | 0                                                              | 0          |
|          | Parkinson's disease                            | 16                                                                      | 34         | 2           | 3          | 37                | 0                                                              | 0          |
|          | Parkinsonian gait                              | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Parkinsonian rest tremor                       | 0                                                                       | 0          | 2           | 2          | 2                 | 0                                                              | 0          |
|          | Parkinsonism                                   | 0                                                                       | 2          | 1           | 3          | 5                 | 0                                                              | 0          |
|          | Parosmia                                       | 57                                                                      | 68         | 171         | 436        | 504               | 0                                                              | 0          |
|          | Paroxysmal sympathetic hyperactivity           | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Partial seizures                               | 19                                                                      | 47         | 0           | 2          | 49                | 0                                                              | 0          |
|          | Partial seizures with secondary generalisation | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Patient elopement                              | 0                                                                       | 2          | 0           | 1          | 3                 | 0                                                              | 0          |
|          | Periodic limb movement disorder                | 0                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Peripheral motor neuropathy                    | 3                                                                       | 5          | 1           | 1          | 6                 | 0                                                              | 0          |
|          | Peripheral nerve lesion                        | 3                                                                       | 4          | 1           | 3          | 7                 | 0                                                              | 0          |
|          | Peripheral nerve palsy                         | 2                                                                       | 2          | 0           | 1          | 3                 | 0                                                              | 0          |
|          | Peripheral nerve paresis                       | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Peripheral paralysis                           | 6                                                                       | 10         | 0           | 0          | 10                | 0                                                              | 0          |
|          | Peripheral sensorimotor neuropathy             | 3                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Peripheral sensory neuropathy                  | 8                                                                       | 9          | 3           | 7          | 16                | 0                                                              | 0          |
|          | Peroneal nerve palsy                           | 14                                                                      | 21         | 3           | 12         | 33                | 0                                                              | 0          |
|          | Persistent genital arousal disorder            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Persistent postural-perceptual dizziness       | 2                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Petit mal epilepsy                             | 12                                                                      | 24         | 1           | 1          | 25                | 0                                                              | 0          |
|          | Phantom limb syndrome                          | 0                                                                       | 1          | 6           | 18         | 19                | 0                                                              | 0          |
|          | Piriformis syndrome                            | 0                                                                       | 1          | 2           | 2          | 3                 | 0                                                              | 0          |
|          | Pleocytosis                                    | 3                                                                       | 7          | 1           | 2          | 9                 | 0                                                              | 0          |
|          | Polyneuropathy                                 | 38                                                                      | 46         | 4           | 4          | 50                | 0                                                              | 0          |
|          | Polyneuropathy chronic                         | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |

|          |                                                  | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|--------------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                                  | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                               | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Polyneuropathy idiopathic progressive            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Post cardiac arrest syndrome                     | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Post herpetic neuralgia                          | 14                                                                      | 16         | 12          | 26         | 42                | 0                                                              | 0          |
|          | Post polio syndrome                              | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Post-traumatic headache                          | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|          | Posterior reversible encephalopathy syndrome     | 7                                                                       | 12         | 0           | 0          | 12                | 0                                                              | 0          |
|          | Postictal paralysis                              | 1                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Postictal state                                  | 5                                                                       | 13         | 5           | 14         | 27                | 0                                                              | 0          |
|          | Postural tremor                                  | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Preictal state                                   | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Presyncope                                       | 359                                                                     | 473        | 1764        | 2519       | 2992              | 0                                                              | 0          |
|          | Primary cough headache                           | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|          | Primary headache associated with sexual activity | 0                                                                       | 1          | 1           | 2          | 3                 | 0                                                              | 0          |
|          | Progressive supranuclear palsy                   | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Prosopagnosia                                    | 0                                                                       | 1          | 1           | 2          | 3                 | 0                                                              | 0          |
|          | Pseudoparalysis                                  | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Pseudostroke                                     | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Psychogenic seizure                              | 1                                                                       | 2          | 0           | 4          | 6                 | 0                                                              | 0          |
|          | Psychomotor hyperactivity                        | 2                                                                       | 5          | 14          | 44         | 49                | 0                                                              | 0          |
|          | Psychomotor skills impaired                      | 2                                                                       | 4          | 4           | 5          | 9                 | 0                                                              | 0          |
|          | Pudendal canal syndrome                          | 2                                                                       | 2          | 0           | 1          | 3                 | 0                                                              | 0          |
|          | Putamen haemorrhage                              | 2                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Pyramidal tract syndrome                         | 2                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Quadrantanopia                                   | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Quadriparesis                                    | 7                                                                       | 9          | 0           | 0          | 9                 | 0                                                              | 0          |
|          | Quadriplegia                                     | 2                                                                       | 6          | 0           | 0          | 6                 | 0                                                              | 0          |
|          | Radial nerve compression                         | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Radial nerve palsy                               | 4                                                                       | 6          | 2           | 2          | 8                 | 0                                                              | 0          |
|          | Radicular pain                                   | 1                                                                       | 3          | 0           | 5          | 8                 | 0                                                              | 0          |
|          | Radiculitis brachial                             | 6                                                                       | 10         | 4           | 14         | 24                | 0                                                              | 0          |
|          | Radiculopathy                                    | 11                                                                      | 16         | 7           | 13         | 29                | 0                                                              | 0          |
|          | Radiologically isolated syndrome                 | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Reduced facial expression                        | 1                                                                       | 2          | 3           | 13         | 15                | 0                                                              | 0          |
|          | Reflexes abnormal                                | 0                                                                       | 3          | 0           | 3          | 6                 | 0                                                              | 0          |
|          | Relapsing multiple sclerosis                     | 1                                                                       | 2          | 0           | 1          | 3                 | 0                                                              | 0          |
|          | Relapsing-remitting multiple sclerosis           | 6                                                                       | 6          | 0           | 0          | 6                 | 0                                                              | 0          |
|          | Repetitive speech                                | 2                                                                       | 5          | 1           | 6          | 11                | 0                                                              | 0          |
|          | Resting tremor                                   | 1                                                                       | 5          | 2           | 5          | 10                | 0                                                              | 0          |
|          | Restless arm syndrome                            | 1                                                                       | 1          | 3           | 5          | 6                 | 0                                                              | 0          |
|          | Restless legs syndrome                           | 35                                                                      | 43         | 40          | 106        | 149               | 0                                                              | 0          |
|          | Retinal migraine                                 | 4                                                                       | 5          | 3           | 14         | 19                | 0                                                              | 0          |
|          | Retrograde amnesia                               | 1                                                                       | 2          | 1           | 2          | 4                 | 0                                                              | 0          |
|          | Reversed hot-cold sensation                      | 0                                                                       | 0          | 1           | 6          | 6                 | 0                                                              | 0          |
|          | Reversible cerebral vasoconstriction syndrome    | 5                                                                       | 8          | 0           | 0          | 8                 | 0                                                              | 0          |
|          | Reversible ischaemic neurological deficit        | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Right hemisphere deficit syndrome                | 2                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Ruptured cerebral aneurysm                       | 5                                                                       | 11         | 0           | 0          | 11                | 0                                                              | 0          |
|          | Sciatic nerve neuropathy                         | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Sciatic nerve palsy                              | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |

|          |                                            | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|--------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                            | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                         | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Sciatica                                   | 31                                                                      | 34         | 48          | 136        | 170               | 0                                                              | 0          |
|          | Secondary progressive multiple sclerosis   | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Sedation                                   | 4                                                                       | 5          | 14          | 41         | 46                | 0                                                              | 0          |
|          | Seizure                                    | 871                                                                     | 1929       | 103         | 153        | 2082              | 0                                                              | 0          |
|          | Seizure anoxic                             | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Seizure cluster                            | 6                                                                       | 8          | 0           | 0          | 8                 | 0                                                              | 0          |
|          | Seizure like phenomena                     | 23                                                                      | 110        | 2           | 10         | 120               | 0                                                              | 0          |
|          | Senile dementia                            | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Sensorimotor disorder                      | 8                                                                       | 14         | 2           | 6          | 20                | 0                                                              | 0          |
|          | Sensory disturbance                        | 60                                                                      | 90         | 128         | 281        | 371               | 0                                                              | 0          |
|          | Sensory integrative dysfunction            | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Sensory loss                               | 52                                                                      | 89         | 52          | 145        | 234               | 0                                                              | 0          |
|          | Sensory overload                           | 3                                                                       | 3          | 4           | 5          | 8                 | 0                                                              | 0          |
|          | Sensory processing disorder                | 1                                                                       | 2          | 1           | 1          | 3                 | 0                                                              | 0          |
|          | Serotonin syndrome                         | 2                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Simple partial seizures                    | 1                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Sinus headache                             | 63                                                                      | 70         | 33          | 134        | 204               | 0                                                              | 0          |
|          | Sleep deficit                              | 14                                                                      | 18         | 13          | 58         | 76                | 0                                                              | 0          |
|          | Sleep paralysis                            | 4                                                                       | 7          | 8           | 21         | 28                | 0                                                              | 0          |
|          | Slow response to stimuli                   | 13                                                                      | 18         | 9           | 26         | 44                | 0                                                              | 0          |
|          | Slow speech                                | 18                                                                      | 30         | 9           | 34         | 64                | 0                                                              | 0          |
|          | Small fibre neuropathy                     | 13                                                                      | 16         | 6           | 9          | 25                | 0                                                              | 0          |
|          | Somnolence                                 | 355                                                                     | 500        | 1350        | 3553       | 4053              | 0                                                              | 0          |
|          | Somnolence neonatal                        | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Speech disorder                            | 153                                                                     | 285        | 119         | 365        | 650               | 0                                                              | 0          |
|          | Speech disorder developmental              | 3                                                                       | 3          | 0           | 6          | 9                 | 0                                                              | 0          |
|          | Spinal artery embolism                     | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Spinal cord compression                    | 3                                                                       | 6          | 0           | 1          | 7                 | 0                                                              | 0          |
|          | Spinal cord disorder                       | 6                                                                       | 9          | 0           | 1          | 10                | 0                                                              | 0          |
|          | Spinal cord haemorrhage                    | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Spinal cord infarction                     | 3                                                                       | 7          | 0           | 0          | 7                 | 0                                                              | 0          |
|          | Spinal cord ischaemia                      | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Spinal cord oedema                         | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Spinal epidural haematoma                  | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Spinal stroke                              | 0                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Spinal subarachnoid haemorrhage            | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Spinal subdural haematoma                  | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Spinal vascular disorder                   | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Spontaneous cerebrospinal fluid leak syndr | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Status epilepticus                         | 21                                                                      | 61         | 3           | 4          | 65                | 0                                                              | 0          |
|          | Status migrainosus                         | 4                                                                       | 5          | 1           | 3          | 8                 | 0                                                              | 0          |
|          | Stiff leg syndrome                         | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Stiff person syndrome                      | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Stroke in evolution                        | 1                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Stupor                                     | 6                                                                       | 8          | 8           | 15         | 23                | 0                                                              | 0          |
|          | Subacute combined cord degeneration        | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Subacute inflammatory demyelinating poly   | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Subarachnoid haemorrhage                   | 47                                                                      | 91         | 0           | 0          | 91                | 0                                                              | 0          |
|          | Subdural effusion                          | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |

|          |                                    | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                    | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                 | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Subdural hygroma                   | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Sudden onset of sleep              | 3                                                                       | 7          | 2           | 2          | 9                 | 0                                                              | 0          |
|          | Superior sagittal sinus thrombosis | 9                                                                       | 16         | 0           | 0          | 16                | 0                                                              | 0          |
|          | Sympathicotonia                    | 0                                                                       | 0          | 2           | 2          | 2                 | 0                                                              | 0          |
|          | Sympathomimetic effect             | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Synaesthesia                       | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Syncope                            | 2309                                                                    | 5565       | 337         | 781        | 6346              | 0                                                              | 0          |
|          | Tardive dyskinesia                 | 2                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Taste disorder                     | 73                                                                      | 100        | 280         | 872        | 972               | 0                                                              | 0          |
|          | Tension headache                   | 119                                                                     | 138        | 77          | 184        | 322               | 0                                                              | 0          |
|          | Thalamic infarction                | 6                                                                       | 21         | 0           | 0          | 21                | 0                                                              | 0          |
|          | Thalamus haemorrhage               | 4                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Thecal sac compression             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Thoracic outlet syndrome           | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|          | Thrombotic cerebral infarction     | 3                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Thrombotic stroke                  | 8                                                                       | 11         | 0           | 0          | 11                | 0                                                              | 0          |
|          | Thunderclap headache               | 2                                                                       | 5          | 1           | 5          | 10                | 0                                                              | 0          |
|          | Tinel's sign                       | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Tongue biting                      | 8                                                                       | 15         | 10          | 28         | 43                | 0                                                              | 0          |
|          | Tongue paralysis                   | 15                                                                      | 24         | 4           | 4          | 28                | 0                                                              | 0          |
|          | Tonic clonic movements             | 9                                                                       | 24         | 1           | 4          | 28                | 0                                                              | 0          |
|          | Tonic convulsion                   | 13                                                                      | 20         | 0           | 0          | 20                | 0                                                              | 0          |
|          | Tonic posturing                    | 0                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Toxic encephalopathy               | 9                                                                       | 18         | 0           | 0          | 18                | 0                                                              | 0          |
|          | Transient aphasia                  | 2                                                                       | 3          | 0           | 1          | 4                 | 0                                                              | 0          |
|          | Transient global amnesia           | 17                                                                      | 33         | 3           | 11         | 44                | 0                                                              | 0          |
|          | Transient ischaemic attack         | 160                                                                     | 384        | 10          | 13         | 397               | 0                                                              | 0          |
|          | Transverse sinus stenosis          | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Transverse sinus thrombosis        | 7                                                                       | 21         | 1           | 1          | 22                | 0                                                              | 0          |
|          | Tremor                             | 798                                                                     | 1122       | 1018        | 4517       | 5639              | 0                                                              | 0          |
|          | Trigeminal nerve disorder          | 2                                                                       | 4          | 7           | 14         | 18                | 0                                                              | 0          |
|          | Trigeminal nerve paresis           | 2                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Trigeminal neuralgia               | 34                                                                      | 45         | 46          | 96         | 141               | 0                                                              | 0          |
|          | Trigeminal neuritis                | 1                                                                       | 2          | 3           | 5          | 7                 | 0                                                              | 0          |
|          | Trigeminal palsy                   | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Tunnel vision                      | 14                                                                      | 97         | 8           | 26         | 123               | 0                                                              | 0          |
|          | Typical aura without headache      | 2                                                                       | 2          | 1           | 2          | 4                 | 0                                                              | 0          |
|          | Uhthoff's phenomenon               | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Ulnar nerve palsy                  | 2                                                                       | 2          | 1           | 1          | 3                 | 0                                                              | 0          |
|          | Ulnar neuritis                     | 0                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Unresponsive to stimuli            | 240                                                                     | 995        | 16          | 93         | 1088              | 0                                                              | 0          |
|          | Upper motor neurone lesion         | 4                                                                       | 8          | 0           | 0          | 8                 | 0                                                              | 0          |
|          | Vlth nerve disorder                | 0                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Vlth nerve paralysis               | 12                                                                      | 35         | 0           | 0          | 35                | 0                                                              | 0          |
|          | Vlth nerve paresis                 | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Vagus nerve disorder               | 2                                                                       | 4          | 2           | 2          | 6                 | 0                                                              | 0          |
|          | Vascular dementia                  | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Vascular encephalopathy            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Vascular headache                  | 3                                                                       | 4          | 1           | 3          | 7                 | 0                                                              | 0          |

|                                                |                                             | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|------------------------------------------------|---------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|                                                |                                             | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM                                       | PT                                          | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|                                                | Vasogenic cerebral oedema                   | 2                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|                                                | Vertebral artery dissection                 | 9                                                                       | 11         | 0           | 0          | 11                | 0                                                              | 0          |
|                                                | Vertebral artery occlusion                  | 5                                                                       | 7          | 0           | 0          | 7                 | 0                                                              | 0          |
|                                                | Vertebral artery stenosis                   | 3                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|                                                | Vertebral artery thrombosis                 | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                                | Vertebrobasilar insufficiency               | 2                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|                                                | Vertebrobasilar stroke                      | 1                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|                                                | Vertigo CNS origin                          | 2                                                                       | 2          | 2           | 4          | 6                 | 0                                                              | 0          |
|                                                | Vestibular migraine                         | 8                                                                       | 8          | 6           | 10         | 18                | 0                                                              | 0          |
|                                                | Vestibular nystagmus                        | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|                                                | Vibratory sense increased                   | 3                                                                       | 3          | 2           | 7          | 10                | 0                                                              | 0          |
|                                                | Visuospatial deficit                        | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                                | Vocal cord paralysis                        | 2                                                                       | 5          | 1           | 1          | 6                 | 0                                                              | 0          |
|                                                | Vocal cord paresis                          | 1                                                                       | 2          | 2           | 3          | 5                 | 0                                                              | 0          |
|                                                | Wernicke's encephalopathy                   | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                                                | White matter lesion                         | 18                                                                      | 40         | 4           | 4          | 44                | 0                                                              | 0          |
| No SOC                                         | *** SOC TOTAL ***                           | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|                                                |                                             | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
| Pregnancy, puerperium and perinatal conditions | *** SOC TOTAL ***                           | 551                                                                     | 993        | 89          | 216        | 1209              | 0                                                              | 0          |
|                                                | Abnormal cord insertion                     | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                                | Abnormal labour                             | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|                                                | Abortion                                    | 6                                                                       | 9          | 0           | 0          | 9                 | 0                                                              | 0          |
|                                                | Abortion early                              | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|                                                | Abortion late                               | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                                | Abortion missed                             | 12                                                                      | 19         | 0           | 0          | 19                | 0                                                              | 0          |
|                                                | Abortion of ectopic pregnancy               | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                                | Abortion spontaneous                        | 192                                                                     | 438        | 4           | 14         | 452               | 0                                                              | 0          |
|                                                | Abortion spontaneous incomplete             | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                                | Abortion threatened                         | 6                                                                       | 6          | 0           | 0          | 6                 | 0                                                              | 0          |
|                                                | Amniorrhexis                                | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                                | Amniorrhea                                  | 2                                                                       | 6          | 1           | 1          | 7                 | 0                                                              | 0          |
|                                                | Amniotic cavity disorder                    | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                                | Anembryonic gestation                       | 4                                                                       | 9          | 1           | 2          | 11                | 0                                                              | 0          |
|                                                | Arrested labour                             | 0                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|                                                | Biochemical pregnancy                       | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|                                                | Breech delivery                             | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                                | Breech presentation                         | 2                                                                       | 2          | 1           | 1          | 3                 | 0                                                              | 0          |
|                                                | Cervical dilatation                         | 4                                                                       | 4          | 1           | 1          | 5                 | 0                                                              | 0          |
|                                                | Cervical incompetence                       | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                                | Chorioamniotic separation                   | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                                | Complication of pregnancy                   | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                                                | Decidual cast                               | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                                | Delivery                                    | 14                                                                      | 17         | 4           | 5          | 22                | 0                                                              | 0          |
|                                                | Eclampsia                                   | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                                | Ectopic pregnancy                           | 6                                                                       | 11         | 0           | 0          | 11                | 0                                                              | 0          |
|                                                | Ectopic pregnancy with contraceptive device | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                                | Failed induction of labour                  | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|                                                | First trimester pregnancy                   | 0                                                                       | 0          | 1           | 6          | 6                 | 0                                                              | 0          |
|                                                | Foetal cardiac disorder                     | 2                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |

|          |                                           | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|-------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                           | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                        | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Foetal death                              | 31                                                                      | 62         | 0           | 0          | 62                | 0                                                              | 0          |
|          | Foetal disorder                           | 7                                                                       | 11         | 0           | 0          | 11                | 0                                                              | 0          |
|          | Foetal growth abnormality                 | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Foetal growth restriction                 | 12                                                                      | 18         | 0           | 0          | 18                | 0                                                              | 0          |
|          | Foetal hypokinesia                        | 13                                                                      | 23         | 0           | 0          | 23                | 0                                                              | 0          |
|          | Foetal macrosomia                         | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Foetal vascular malperfusion              | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Gestational diabetes                      | 4                                                                       | 9          | 0           | 0          | 9                 | 0                                                              | 0          |
|          | Gestational hypertension                  | 4                                                                       | 6          | 0           | 2          | 8                 | 0                                                              | 0          |
|          | HELLP syndrome                            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Haemorrhage in pregnancy                  | 20                                                                      | 31         | 0           | 2          | 33                | 0                                                              | 0          |
|          | High risk pregnancy                       | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Hydrops foetalis                          | 1                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Induced labour                            | 11                                                                      | 20         | 0           | 1          | 21                | 0                                                              | 0          |
|          | Jaundice neonatal                         | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Labour complication                       | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Labour pain                               | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Live birth                                | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Low birth weight baby                     | 1                                                                       | 3          | 2           | 2          | 5                 | 0                                                              | 0          |
|          | Meconium in amniotic fluid                | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Meconium stain                            | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Morning sickness                          | 4                                                                       | 4          | 6           | 11         | 15                | 0                                                              | 0          |
|          | Neonatal disorder                         | 0                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Normal foetus                             | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Normal labour                             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Normal newborn                            | 0                                                                       | 0          | 2           | 2          | 2                 | 0                                                              | 0          |
|          | Oligohydramnios                           | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Pelvic girdle pain                        | 0                                                                       | 0          | 0           | 3          | 3                 | 0                                                              | 0          |
|          | Peripartum cardiomyopathy                 | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Placenta accreta                          | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Placenta praevia                          | 2                                                                       | 4          | 0           | 1          | 5                 | 0                                                              | 0          |
|          | Placenta praevia haemorrhage              | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Placental calcification                   | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Placental disorder                        | 3                                                                       | 4          | 0           | 1          | 5                 | 0                                                              | 0          |
|          | Placental infarction                      | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Placental insufficiency                   | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Polyhydramnios                            | 3                                                                       | 6          | 0           | 0          | 6                 | 0                                                              | 0          |
|          | Poor weight gain neonatal                 | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Post abortion haemorrhage                 | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Postpartum disorder                       | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Postpartum haemorrhage                    | 3                                                                       | 7          | 1           | 4          | 11                | 0                                                              | 0          |
|          | Postpartum state                          | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Pre-eclampsia                             | 14                                                                      | 18         | 0           | 1          | 19                | 0                                                              | 0          |
|          | Precipitate labour                        | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Pregnancy                                 | 6                                                                       | 6          | 38          | 88         | 94                | 0                                                              | 0          |
|          | Pregnancy after post coital contraception | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Pregnancy on contraceptive                | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Pregnancy on oral contraceptive           | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Pregnancy with advanced maternal age      | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |

|                |                                              | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------------|----------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|                |                                              | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM       | PT                                           | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|                | Pregnancy with contraceptive device          | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                | Premature baby                               | 14                                                                      | 16         | 2           | 4          | 20                | 0                                                              | 0          |
|                | Premature delivery                           | 18                                                                      | 27         | 2           | 5          | 32                | 0                                                              | 0          |
|                | Premature labour                             | 21                                                                      | 32         | 1           | 6          | 38                | 0                                                              | 0          |
|                | Premature rupture of membranes               | 10                                                                      | 14         | 2           | 3          | 17                | 0                                                              | 0          |
|                | Premature separation of placenta             | 10                                                                      | 15         | 1           | 1          | 16                | 0                                                              | 0          |
|                | Preterm premature rupture of membranes       | 6                                                                       | 11         | 0           | 1          | 12                | 0                                                              | 0          |
|                | Prolonged labour                             | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                | Prolonged pregnancy                          | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                | Retained placenta or membranes               | 2                                                                       | 3          | 0           | 1          | 4                 | 0                                                              | 0          |
|                | Ruptured ectopic pregnancy                   | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                | Second trimester pregnancy                   | 0                                                                       | 2          | 0           | 1          | 3                 | 0                                                              | 0          |
|                | Shoulder dystocia                            | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                | Somatic symptom disorder of pregnancy        | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|                | Stillbirth                                   | 13                                                                      | 21         | 1           | 1          | 22                | 0                                                              | 0          |
|                | Subchorionic haematoma                       | 1                                                                       | 4          | 0           | 1          | 5                 | 0                                                              | 0          |
|                | Subchorionic haemorrhage                     | 1                                                                       | 1          | 1           | 3          | 4                 | 0                                                              | 0          |
|                | Term baby                                    | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                | Threatened labour                            | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                | Twin pregnancy                               | 2                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|                | Umbilical cord abnormality                   | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                | Umbilical cord around neck                   | 0                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|                | Umbilical cord prolapse                      | 0                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                | Umbilical cord short                         | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|                | Umbilical granuloma                          | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|                | Unintended pregnancy                         | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                | Unwanted pregnancy                           | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|                | Uterine atony                                | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                | Uterine contractions abnormal                | 5                                                                       | 5          | 3           | 5          | 10                | 0                                                              | 0          |
|                | Uterine contractions during pregnancy        | 11                                                                      | 11         | 5           | 13         | 24                | 0                                                              | 0          |
|                | Uterine hypertonus                           | 3                                                                       | 4          | 1           | 2          | 6                 | 0                                                              | 0          |
| Product issues | *** SOC TOTAL ***                            | 23                                                                      | 34         | 518         | 2152       | 2186              | 0                                                              | 0          |
|                | Device breakage                              | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|                | Device connection issue                      | 1                                                                       | 1          | 44          | 400        | 401               | 0                                                              | 0          |
|                | Device defective                             | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|                | Device dislocation                           | 2                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|                | Device expulsion                             | 1                                                                       | 2          | 1           | 1          | 3                 | 0                                                              | 0          |
|                | Device failure                               | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                | Device infusion issue                        | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                | Device issue                                 | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|                | Device leakage                               | 2                                                                       | 2          | 0           | 2          | 4                 | 0                                                              | 0          |
|                | Device malfunction                           | 1                                                                       | 3          | 0           | 7          | 10                | 0                                                              | 0          |
|                | Device occlusion                             | 1                                                                       | 3          | 3           | 3          | 6                 | 0                                                              | 0          |
|                | Device physical property issue               | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|                | Device temperature issue                     | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|                | Drug delivery system malfunction             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                | Electromagnetic interference                 | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|                | Inappropriate release of product for distrib | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|                | Liquid product physical issue                | 0                                                                       | 0          | 10          | 15         | 15                | 0                                                              | 0          |

|                       |                                      | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|-----------------------|--------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|                       |                                      | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM              | PT                                   | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|                       | Manufacturing issue                  | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|                       | Manufacturing materials issue        | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                       | Manufacturing product shipping issue | 0                                                                       | 0          | 0           | 3          | 3                 | 0                                                              | 0          |
|                       | Needle issue                         | 0                                                                       | 1          | 3           | 67         | 68                | 0                                                              | 0          |
|                       | Oversensing                          | 0                                                                       | 0          | 2           | 6          | 6                 | 0                                                              | 0          |
|                       | Product after taste                  | 0                                                                       | 0          | 3           | 11         | 11                | 0                                                              | 0          |
|                       | Product availability issue           | 0                                                                       | 0          | 17          | 55         | 55                | 0                                                              | 0          |
|                       | Product barcode issue                | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|                       | Product closure issue                | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|                       | Product colour issue                 | 0                                                                       | 0          | 8           | 20         | 20                | 0                                                              | 0          |
|                       | Product complaint                    | 0                                                                       | 0          | 0           | 3          | 3                 | 0                                                              | 0          |
|                       | Product container issue              | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|                       | Product container seal issue         | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|                       | Product contamination                | 1                                                                       | 2          | 7           | 8          | 10                | 0                                                              | 0          |
|                       | Product contamination physical       | 2                                                                       | 2          | 14          | 41         | 43                | 0                                                              | 0          |
|                       | Product delivery mechanism issue     | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|                       | Product expiration date issue        | 0                                                                       | 0          | 4           | 7          | 7                 | 0                                                              | 0          |
|                       | Product identification number issue  | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|                       | Product impurity                     | 0                                                                       | 0          | 1           | 4          | 4                 | 0                                                              | 0          |
|                       | Product label issue                  | 1                                                                       | 1          | 6           | 9          | 10                | 0                                                              | 0          |
|                       | Product leakage                      | 0                                                                       | 0          | 0           | 8          | 8                 | 0                                                              | 0          |
|                       | Product lot number issue             | 1                                                                       | 1          | 2           | 2          | 3                 | 0                                                              | 0          |
|                       | Product origin unknown               | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|                       | Product packaging issue              | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|                       | Product packaging quantity issue     | 0                                                                       | 0          | 1           | 7          | 7                 | 0                                                              | 0          |
|                       | Product physical issue               | 0                                                                       | 0          | 3           | 7          | 7                 | 0                                                              | 0          |
|                       | Product quality issue                | 1                                                                       | 1          | 69          | 75         | 76                | 0                                                              | 0          |
|                       | Product substitution issue           | 0                                                                       | 0          | 1           | 4          | 4                 | 0                                                              | 0          |
|                       | Product supply issue                 | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|                       | Product tampering                    | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                       | Product taste abnormal               | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|                       | Product temperature excursion issue  | 0                                                                       | 0          | 289         | 984        | 984               | 0                                                              | 0          |
|                       | Prosthetic cardiac valve malfunction | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                       | Recalled product                     | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                       | Stent malfunction                    | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                       | Suspected counterfeit product        | 0                                                                       | 0          | 1           | 3          | 3                 | 0                                                              | 0          |
|                       | Suspected product contamination      | 0                                                                       | 0          | 2           | 2          | 2                 | 0                                                              | 0          |
|                       | Suspected product quality issue      | 0                                                                       | 0          | 10          | 11         | 11                | 0                                                              | 0          |
|                       | Syringe issue                        | 0                                                                       | 1          | 10          | 364        | 365               | 0                                                              | 0          |
|                       | Thrombosis in device                 | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                       | Undersensing                         | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
| Psychiatric disorders | *** SOC TOTAL ***                    | 3610                                                                    | 5963       | 5095        | 16800      | 22763             | 0                                                              | 0          |
|                       | Abnormal behaviour                   | 24                                                                      | 60         | 17          | 75         | 135               | 0                                                              | 0          |
|                       | Abnormal dreams                      | 16                                                                      | 21         | 67          | 198        | 219               | 0                                                              | 0          |
|                       | Abnormal sleep-related event         | 1                                                                       | 2          | 1           | 5          | 7                 | 0                                                              | 0          |
|                       | Abulia                               | 1                                                                       | 2          | 1           | 1          | 3                 | 0                                                              | 0          |
|                       | Acute psychosis                      | 3                                                                       | 7          | 0           | 0          | 7                 | 0                                                              | 0          |
|                       | Acute stress disorder                | 0                                                                       | 1          | 7           | 9          | 10                | 0                                                              | 0          |
|                       | Adjustment disorder                  | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |



|          |                                             | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|---------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                             | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                          | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Adjustment disorder with depressed mood     | 5                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Affect lability                             | 4                                                                       | 4          | 8           | 19         | 23                | 0                                                              | 0          |
|          | Affective disorder                          | 2                                                                       | 2          | 0           | 9          | 11                | 0                                                              | 0          |
|          | Aggression                                  | 20                                                                      | 49         | 15          | 41         | 90                | 0                                                              | 0          |
|          | Agitation                                   | 44                                                                      | 79         | 59          | 190        | 269               | 0                                                              | 0          |
|          | Agoraphobia                                 | 3                                                                       | 4          | 0           | 1          | 5                 | 0                                                              | 0          |
|          | Alcohol abuse                               | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Alcohol problem                             | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|          | Alcohol withdrawal syndrome                 | 1                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Alcoholic hangover                          | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Alcoholism                                  | 3                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Alice in wonderland syndrome                | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Anger                                       | 14                                                                      | 24         | 25          | 83         | 107               | 0                                                              | 0          |
|          | Anorgasmia                                  | 2                                                                       | 2          | 0           | 1          | 3                 | 0                                                              | 0          |
|          | Anticipatory anxiety                        | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Antisocial behaviour                        | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Anxiety                                     | 285                                                                     | 394        | 608         | 2255       | 2649              | 0                                                              | 0          |
|          | Anxiety disorder                            | 4                                                                       | 6          | 4           | 14         | 20                | 0                                                              | 0          |
|          | Apathy                                      | 15                                                                      | 27         | 60          | 82         | 109               | 0                                                              | 0          |
|          | Aphonia psychogenic                         | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Attention deficit hyperactivity disorder    | 5                                                                       | 6          | 4           | 8          | 14                | 0                                                              | 0          |
|          | Autism spectrum disorder                    | 1                                                                       | 3          | 1           | 2          | 5                 | 0                                                              | 0          |
|          | Autoscopy                                   | 1                                                                       | 3          | 2           | 20         | 23                | 0                                                              | 0          |
|          | Aversion                                    | 1                                                                       | 1          | 2           | 4          | 5                 | 0                                                              | 0          |
|          | Behaviour disorder                          | 1                                                                       | 4          | 3           | 8          | 12                | 0                                                              | 0          |
|          | Belligerence                                | 1                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Binge drinking                              | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Binge eating                                | 0                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Bipolar I disorder                          | 2                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Bipolar disorder                            | 5                                                                       | 10         | 1           | 1          | 11                | 0                                                              | 0          |
|          | Blunted affect                              | 0                                                                       | 1          | 2           | 2          | 3                 | 0                                                              | 0          |
|          | Body dysmorphic disorder                    | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Borderline personality disorder             | 2                                                                       | 2          | 0           | 1          | 3                 | 0                                                              | 0          |
|          | Boredom                                     | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Bradyphrenia                                | 11                                                                      | 18         | 23          | 51         | 69                | 0                                                              | 0          |
|          | Breath holding                              | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Breathing-related sleep disorder            | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Brief psychotic disorder with marked stress | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Bruxism                                     | 7                                                                       | 9          | 10          | 33         | 42                | 0                                                              | 0          |
|          | Burnout syndrome                            | 1                                                                       | 1          | 2           | 2          | 3                 | 0                                                              | 0          |
|          | Cardiovascular somatic symptom disorder     | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Catastrophic reaction                       | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Catatonia                                   | 1                                                                       | 6          | 1           | 7          | 13                | 0                                                              | 0          |
|          | Change in sustained attention               | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Claustrophobia                              | 0                                                                       | 0          | 1           | 6          | 6                 | 0                                                              | 0          |
|          | Clinomania                                  | 0                                                                       | 0          | 1           | 4          | 4                 | 0                                                              | 0          |
|          | Communication disorder                      | 16                                                                      | 38         | 6           | 26         | 64                | 0                                                              | 0          |
|          | Completed suicide                           | 7                                                                       | 14         | 0           | 0          | 14                | 0                                                              | 0          |
|          | Confabulation                               | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |

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|----------|------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                          | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                       | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Confusional state                        | 503                                                                     | 930        | 418         | 1490       | 2420              | 0                                                              | 0          |
|          | Constricted affect                       | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|          | Conversion disorder                      | 10                                                                      | 16         | 6           | 13         | 29                | 0                                                              | 0          |
|          | Daydreaming                              | 0                                                                       | 0          | 6           | 17         | 17                | 0                                                              | 0          |
|          | Decreased eye contact                    | 1                                                                       | 2          | 1           | 3          | 5                 | 0                                                              | 0          |
|          | Decreased interest                       | 1                                                                       | 2          | 3           | 15         | 17                | 0                                                              | 0          |
|          | Defiant behaviour                        | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Deja vu                                  | 0                                                                       | 1          | 0           | 2          | 3                 | 0                                                              | 0          |
|          | Delirium                                 | 96                                                                      | 261        | 10          | 24         | 285               | 0                                                              | 0          |
|          | Delirium febrile                         | 7                                                                       | 12         | 2           | 2          | 14                | 0                                                              | 0          |
|          | Delirium tremens                         | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Delusion                                 | 11                                                                      | 29         | 10          | 41         | 70                | 0                                                              | 0          |
|          | Delusion of grandeur                     | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Delusion of parasitosis                  | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Delusional disorder, erotomanic type     | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Delusional disorder, persecutory type    | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Delusional disorder, unspecified type    | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|          | Delusional perception                    | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Depersonalisation/derealisation disorder | 4                                                                       | 4          | 1           | 6          | 10                | 0                                                              | 0          |
|          | Depressed mood                           | 80                                                                      | 90         | 141         | 308        | 398               | 0                                                              | 0          |
|          | Depression                               | 113                                                                     | 154        | 159         | 372        | 526               | 0                                                              | 0          |
|          | Depression suicidal                      | 3                                                                       | 6          | 0           | 0          | 6                 | 0                                                              | 0          |
|          | Depressive symptom                       | 1                                                                       | 2          | 5           | 8          | 10                | 0                                                              | 0          |
|          | Derealisation                            | 6                                                                       | 7          | 9           | 15         | 22                | 0                                                              | 0          |
|          | Dermatillomania                          | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Discouragement                           | 0                                                                       | 2          | 2           | 4          | 6                 | 0                                                              | 0          |
|          | Disinhibition                            | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Disorganised speech                      | 6                                                                       | 11         | 6           | 27         | 38                | 0                                                              | 0          |
|          | Disorientation                           | 138                                                                     | 245        | 138         | 672        | 917               | 0                                                              | 0          |
|          | Dissociation                             | 11                                                                      | 16         | 10          | 41         | 57                | 0                                                              | 0          |
|          | Dissociative amnesia                     | 0                                                                       | 0          | 0           | 4          | 4                 | 0                                                              | 0          |
|          | Dissociative disorder                    | 0                                                                       | 2          | 0           | 2          | 4                 | 0                                                              | 0          |
|          | Distractibility                          | 0                                                                       | 1          | 2           | 8          | 9                 | 0                                                              | 0          |
|          | Disturbance in sexual arousal            | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Disturbance in social behaviour          | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Drug abuse                               | 4                                                                       | 7          | 0           | 1          | 8                 | 0                                                              | 0          |
|          | Drug dependence                          | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Dysphemia                                | 9                                                                       | 17         | 6           | 34         | 51                | 0                                                              | 0          |
|          | Dysphoria                                | 8                                                                       | 8          | 82          | 93         | 101               | 0                                                              | 0          |
|          | Eating disorder                          | 11                                                                      | 12         | 32          | 134        | 146               | 0                                                              | 0          |
|          | Emetophobia                              | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Emotional disorder                       | 14                                                                      | 21         | 18          | 56         | 77                | 0                                                              | 0          |
|          | Emotional distress                       | 25                                                                      | 37         | 20          | 103        | 140               | 0                                                              | 0          |
|          | Emotional poverty                        | 1                                                                       | 1          | 3           | 6          | 7                 | 0                                                              | 0          |
|          | Enuresis                                 | 12                                                                      | 15         | 8           | 20         | 35                | 0                                                              | 0          |
|          | Euphoric mood                            | 7                                                                       | 10         | 26          | 95         | 105               | 0                                                              | 0          |
|          | Executive dysfunction                    | 2                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Exhibitionism                            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Exploding head syndrome                  | 0                                                                       | 0          | 1           | 6          | 6                 | 0                                                              | 0          |

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|----------|-----------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                         | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                      | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Factitious disorder                     | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Fear                                    | 31                                                                      | 49         | 80          | 207        | 256               | 0                                                              | 0          |
|          | Fear of death                           | 2                                                                       | 4          | 16          | 27         | 31                | 0                                                              | 0          |
|          | Fear of disease                         | 0                                                                       | 0          | 5           | 10         | 10                | 0                                                              | 0          |
|          | Fear of eating                          | 2                                                                       | 2          | 0           | 6          | 8                 | 0                                                              | 0          |
|          | Fear of falling                         | 0                                                                       | 0          | 3           | 7          | 7                 | 0                                                              | 0          |
|          | Fear of injection                       | 1                                                                       | 1          | 14          | 58         | 59                | 0                                                              | 0          |
|          | Fear of open spaces                     | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Fear-related avoidance of activities    | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Feeling guilty                          | 0                                                                       | 0          | 3           | 4          | 4                 | 0                                                              | 0          |
|          | Feeling of despair                      | 8                                                                       | 10         | 21          | 31         | 41                | 0                                                              | 0          |
|          | Feelings of worthlessness               | 1                                                                       | 1          | 2           | 4          | 5                 | 0                                                              | 0          |
|          | Female orgasmic disorder                | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|          | Flashback                               | 0                                                                       | 0          | 1           | 3          | 3                 | 0                                                              | 0          |
|          | Flat affect                             | 1                                                                       | 3          | 1           | 5          | 8                 | 0                                                              | 0          |
|          | Flight of ideas                         | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Frustration tolerance decreased         | 12                                                                      | 15         | 14          | 36         | 51                | 0                                                              | 0          |
|          | Generalised anxiety disorder            | 3                                                                       | 3          | 0           | 6          | 9                 | 0                                                              | 0          |
|          | Genito-pelvic pain/penetration disorder | 1                                                                       | 1          | 1           | 2          | 3                 | 0                                                              | 0          |
|          | Grief reaction                          | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Habit cough                             | 2                                                                       | 2          | 2           | 3          | 5                 | 0                                                              | 0          |
|          | Hallucination                           | 196                                                                     | 501        | 14          | 49         | 550               | 0                                                              | 0          |
|          | Hallucination, auditory                 | 22                                                                      | 56         | 7           | 10         | 66                | 0                                                              | 0          |
|          | Hallucination, olfactory                | 3                                                                       | 6          | 1           | 1          | 7                 | 0                                                              | 0          |
|          | Hallucination, tactile                  | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Hallucination, visual                   | 19                                                                      | 62         | 6           | 10         | 72                | 0                                                              | 0          |
|          | Hallucinations, mixed                   | 3                                                                       | 10         | 0           | 1          | 11                | 0                                                              | 0          |
|          | Haphephobia                             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Head banging                            | 9                                                                       | 9          | 5           | 9          | 18                | 0                                                              | 0          |
|          | Helplessness                            | 1                                                                       | 2          | 0           | 5          | 7                 | 0                                                              | 0          |
|          | Histrionic personality disorder         | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Homicidal ideation                      | 2                                                                       | 2          | 0           | 1          | 3                 | 0                                                              | 0          |
|          | Hostility                               | 1                                                                       | 1          | 0           | 4          | 5                 | 0                                                              | 0          |
|          | Hyperarousal                            | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|          | Hypervigilance                          | 1                                                                       | 1          | 2           | 12         | 13                | 0                                                              | 0          |
|          | Hypnagogic hallucination                | 1                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Hypomania                               | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Illogical thinking                      | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|          | Illusion                                | 6                                                                       | 7          | 10          | 17         | 24                | 0                                                              | 0          |
|          | Immunisation anxiety related reaction   | 8                                                                       | 9          | 4           | 13         | 22                | 0                                                              | 0          |
|          | Impaired reasoning                      | 2                                                                       | 3          | 1           | 3          | 6                 | 0                                                              | 0          |
|          | Impatience                              | 1                                                                       | 2          | 0           | 3          | 5                 | 0                                                              | 0          |
|          | Imperception                            | 0                                                                       | 0          | 2           | 4          | 4                 | 0                                                              | 0          |
|          | Impulse-control disorder                | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Impulsive behaviour                     | 2                                                                       | 2          | 1           | 4          | 6                 | 0                                                              | 0          |
|          | Inappropriate affect                    | 4                                                                       | 4          | 3           | 15         | 19                | 0                                                              | 0          |
|          | Indifference                            | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Initial insomnia                        | 8                                                                       | 11         | 21          | 53         | 64                | 0                                                              | 0          |
|          | Insomnia                                | 494                                                                     | 605        | 1268        | 3556       | 4161              | 0                                                              | 0          |

|          |                                             | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|---------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                             | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                          | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Intentional self-injury                     | 2                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Intrusive thoughts                          | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Irritability                                | 46                                                                      | 60         | 93          | 248        | 308               | 0                                                              | 0          |
|          | Jamais vu                                   | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Lack of spontaneous speech                  | 0                                                                       | 3          | 1           | 5          | 8                 | 0                                                              | 0          |
|          | Laziness                                    | 0                                                                       | 0          | 4           | 24         | 24                | 0                                                              | 0          |
|          | Learning disability                         | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|          | Learning disorder                           | 0                                                                       | 0          | 2           | 2          | 2                 | 0                                                              | 0          |
|          | Libido decreased                            | 5                                                                       | 6          | 13          | 20         | 26                | 0                                                              | 0          |
|          | Libido disorder                             | 0                                                                       | 0          | 3           | 3          | 3                 | 0                                                              | 0          |
|          | Libido increased                            | 0                                                                       | 0          | 3           | 5          | 5                 | 0                                                              | 0          |
|          | Limited symptom panic attack                | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Listless                                    | 12                                                                      | 12         | 37          | 76         | 88                | 0                                                              | 0          |
|          | Logorrhoia                                  | 1                                                                       | 1          | 5           | 13         | 14                | 0                                                              | 0          |
|          | Loose associations                          | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Loss of dreaming                            | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Loss of libido                              | 6                                                                       | 7          | 8           | 11         | 18                | 0                                                              | 0          |
|          | Major depression                            | 10                                                                      | 19         | 2           | 2          | 21                | 0                                                              | 0          |
|          | Mania                                       | 4                                                                       | 9          | 6           | 25         | 34                | 0                                                              | 0          |
|          | Manic symptom                               | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Mental disorder                             | 22                                                                      | 32         | 23          | 70         | 102               | 0                                                              | 0          |
|          | Mental disorder due to a general medical co | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Mental fatigue                              | 30                                                                      | 37         | 16          | 36         | 73                | 0                                                              | 0          |
|          | Mental status changes                       | 155                                                                     | 321        | 13          | 67         | 388               | 0                                                              | 0          |
|          | Middle insomnia                             | 13                                                                      | 16         | 23          | 36         | 52                | 0                                                              | 0          |
|          | Mixed anxiety and depressive disorder       | 1                                                                       | 3          | 1           | 1          | 4                 | 0                                                              | 0          |
|          | Mood altered                                | 18                                                                      | 20         | 31          | 66         | 86                | 0                                                              | 0          |
|          | Mood disorder due to a general medical co   | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Mood swings                                 | 13                                                                      | 16         | 48          | 75         | 91                | 0                                                              | 0          |
|          | Morbid thoughts                             | 2                                                                       | 2          | 0           | 3          | 5                 | 0                                                              | 0          |
|          | Mutism                                      | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Near death experience                       | 18                                                                      | 34         | 2           | 4          | 38                | 0                                                              | 0          |
|          | Negative thoughts                           | 2                                                                       | 2          | 0           | 4          | 6                 | 0                                                              | 0          |
|          | Nervousness                                 | 42                                                                      | 59         | 113         | 667        | 726               | 0                                                              | 0          |
|          | Neuropsychiatric symptoms                   | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Neurosis                                    | 0                                                                       | 1          | 2           | 2          | 3                 | 0                                                              | 0          |
|          | Nightmare                                   | 40                                                                      | 48         | 60          | 210        | 258               | 0                                                              | 0          |
|          | Obsessive thoughts                          | 1                                                                       | 1          | 2           | 2          | 3                 | 0                                                              | 0          |
|          | Obsessive-compulsive disorder               | 2                                                                       | 3          | 1           | 1          | 4                 | 0                                                              | 0          |
|          | Obsessive-compulsive symptom                | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Orgasm abnormal                             | 0                                                                       | 0          | 3           | 3          | 3                 | 0                                                              | 0          |
|          | Orgasmic sensation decreased                | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Panic attack                                | 66                                                                      | 84         | 99          | 300        | 384               | 0                                                              | 0          |
|          | Panic disorder                              | 7                                                                       | 9          | 6           | 17         | 26                | 0                                                              | 0          |
|          | Panic reaction                              | 14                                                                      | 19         | 18          | 77         | 96                | 0                                                              | 0          |
|          | Paramnesia                                  | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Paranoia                                    | 8                                                                       | 21         | 8           | 38         | 59                | 0                                                              | 0          |
|          | Parasomnia                                  | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|          | Parkinson's disease psychosis               | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |

|          |                                                   | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|---------------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                                   | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                                | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Paruresis                                         | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Pedantic speech                                   | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Perinatal depression                              | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Persecutory delusion                              | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Perseveration                                     | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Persistent depressive disorder                    | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|          | Personality change                                | 2                                                                       | 4          | 4           | 10         | 14                | 0                                                              | 0          |
|          | Personality disorder                              | 1                                                                       | 2          | 0           | 3          | 5                 | 0                                                              | 0          |
|          | Phantom vibration syndrome                        | 0                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Phobia                                            | 0                                                                       | 0          | 3           | 7          | 7                 | 0                                                              | 0          |
|          | Phobia of driving                                 | 0                                                                       | 0          | 3           | 3          | 3                 | 0                                                              | 0          |
|          | Phonophobia                                       | 1                                                                       | 2          | 3           | 4          | 6                 | 0                                                              | 0          |
|          | Pica                                              | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|          | Polydipsia psychogenic                            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Poor quality sleep                                | 72                                                                      | 84         | 108         | 301        | 385               | 0                                                              | 0          |
|          | Post-traumatic stress disorder                    | 2                                                                       | 3          | 1           | 8          | 11                | 0                                                              | 0          |
|          | Posturing                                         | 0                                                                       | 2          | 0           | 2          | 4                 | 0                                                              | 0          |
|          | Poverty of speech                                 | 1                                                                       | 1          | 0           | 3          | 4                 | 0                                                              | 0          |
|          | Pressure of speech                                | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Pseudohallucination                               | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Psychiatric symptom                               | 3                                                                       | 5          | 2           | 4          | 9                 | 0                                                              | 0          |
|          | Psychogenic movement disorder                     | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Psychogenic pseudosyncope                         | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Psychogenic tremor                                | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Psychological trauma                              | 2                                                                       | 2          | 0           | 2          | 4                 | 0                                                              | 0          |
|          | Psychomotor retardation                           | 1                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Psychotic disorder                                | 18                                                                      | 44         | 10          | 24         | 68                | 0                                                              | 0          |
|          | Psychotic symptom                                 | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Purging                                           | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Rapid eye movements sleep abnormal                | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|          | Reading disorder                                  | 5                                                                       | 6          | 8           | 19         | 25                | 0                                                              | 0          |
|          | Regressive behaviour                              | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Restlessness                                      | 65                                                                      | 95         | 130         | 417        | 512               | 0                                                              | 0          |
|          | Schizoaffective disorder                          | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Schizophrenia                                     | 3                                                                       | 8          | 0           | 1          | 9                 | 0                                                              | 0          |
|          | Selective eating disorder                         | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Self esteem decreased                             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Self-induced vomiting                             | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|          | Self-injurious ideation                           | 2                                                                       | 2          | 2           | 4          | 6                 | 0                                                              | 0          |
|          | Sense of a foreshortened future                   | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Separation anxiety disorder                       | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Shared psychotic disorder                         | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Sleep attacks                                     | 2                                                                       | 2          | 2           | 3          | 5                 | 0                                                              | 0          |
|          | Sleep disorder                                    | 235                                                                     | 343        | 381         | 2248       | 2591              | 0                                                              | 0          |
|          | Sleep disorder due to a general medical condition | 0                                                                       | 0          | 2           | 5          | 5                 | 0                                                              | 0          |
|          | Sleep disorder due to general medical condition   | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|          | Sleep disorder due to general medical condition   | 0                                                                       | 0          | 0           | 3          | 3                 | 0                                                              | 0          |
|          | Sleep inertia                                     | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Sleep talking                                     | 3                                                                       | 4          | 5           | 12         | 16                | 0                                                              | 0          |

|                             |                                           | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|-----------------------------|-------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|                             |                                           | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM                    | PT                                        | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|                             | Sleep terror                              | 4                                                                       | 5          | 3           | 19         | 24                | 0                                                              | 0          |
|                             | Social anxiety disorder                   | 1                                                                       | 1          | 2           | 4          | 5                 | 0                                                              | 0          |
|                             | Social avoidant behaviour                 | 1                                                                       | 2          | 2           | 5          | 7                 | 0                                                              | 0          |
|                             | Social fear                               | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|                             | Soliloquy                                 | 1                                                                       | 1          | 3           | 7          | 8                 | 0                                                              | 0          |
|                             | Somatic hallucination                     | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                             | Somatic symptom disorder                  | 0                                                                       | 0          | 5           | 9          | 9                 | 0                                                              | 0          |
|                             | Somnambulism                              | 4                                                                       | 8          | 1           | 7          | 15                | 0                                                              | 0          |
|                             | Sopor                                     | 1                                                                       | 7          | 0           | 7          | 14                | 0                                                              | 0          |
|                             | Speech sound disorder                     | 1                                                                       | 1          | 2           | 6          | 7                 | 0                                                              | 0          |
|                             | Staring                                   | 15                                                                      | 29         | 6           | 29         | 58                | 0                                                              | 0          |
|                             | Stereotypy                                | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|                             | Stress                                    | 23                                                                      | 30         | 79          | 162        | 192               | 0                                                              | 0          |
|                             | Stubbornness                              | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                             | Substance abuse                           | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                             | Substance-induced psychotic disorder      | 2                                                                       | 2          | 0           | 1          | 3                 | 0                                                              | 0          |
|                             | Suicidal behaviour                        | 1                                                                       | 6          | 0           | 0          | 6                 | 0                                                              | 0          |
|                             | Suicidal ideation                         | 48                                                                      | 120        | 1           | 4          | 124               | 0                                                              | 0          |
|                             | Suicide attempt                           | 7                                                                       | 9          | 0           | 0          | 9                 | 0                                                              | 0          |
|                             | Suspiciousness                            | 0                                                                       | 0          | 1           | 3          | 3                 | 0                                                              | 0          |
|                             | Tachyphrenia                              | 3                                                                       | 3          | 6           | 16         | 19                | 0                                                              | 0          |
|                             | Taciturnity                               | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|                             | Tearfulness                               | 6                                                                       | 8          | 7           | 26         | 34                | 0                                                              | 0          |
|                             | Tension                                   | 10                                                                      | 13         | 33          | 95         | 108               | 0                                                              | 0          |
|                             | Terminal insomnia                         | 6                                                                       | 9          | 3           | 10         | 19                | 0                                                              | 0          |
|                             | Thanatophobia                             | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|                             | Thinking abnormal                         | 13                                                                      | 29         | 28          | 133        | 162               | 0                                                              | 0          |
|                             | Thought blocking                          | 0                                                                       | 0          | 3           | 4          | 4                 | 0                                                              | 0          |
|                             | Tic                                       | 13                                                                      | 15         | 6           | 15         | 30                | 0                                                              | 0          |
|                             | Time perception altered                   | 0                                                                       | 1          | 0           | 6          | 7                 | 0                                                              | 0          |
|                             | Tobacco abuse                             | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                             | Trance                                    | 1                                                                       | 1          | 0           | 2          | 3                 | 0                                                              | 0          |
|                             | Violence-related symptom                  | 1                                                                       | 1          | 1           | 3          | 4                 | 0                                                              | 0          |
|                             | Vomiting psychogenic                      | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
| Renal and urinary disorders | *** SOC TOTAL ***                         | 1493                                                                    | 2418       | 891         | 2301       | 4719              | 0                                                              | 0          |
|                             | Acute kidney injury                       | 326                                                                     | 545        | 4           | 6          | 551               | 0                                                              | 0          |
|                             | Albuminuria                               | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|                             | Anti-glomerular basement membrane disease | 3                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|                             | Anuria                                    | 9                                                                       | 16         | 0           | 0          | 16                | 0                                                              | 0          |
|                             | Atonic urinary bladder                    | 0                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|                             | Azotaemia                                 | 5                                                                       | 7          | 0           | 0          | 7                 | 0                                                              | 0          |
|                             | Bladder dilatation                        | 4                                                                       | 5          | 2           | 5          | 10                | 0                                                              | 0          |
|                             | Bladder discomfort                        | 1                                                                       | 3          | 13          | 22         | 25                | 0                                                              | 0          |
|                             | Bladder disorder                          | 7                                                                       | 9          | 6           | 18         | 27                | 0                                                              | 0          |
|                             | Bladder diverticulum                      | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                             | Bladder dysfunction                       | 3                                                                       | 4          | 1           | 2          | 6                 | 0                                                              | 0          |
|                             | Bladder hypertrophy                       | 5                                                                       | 7          | 0           | 2          | 9                 | 0                                                              | 0          |
|                             | Bladder irritation                        | 1                                                                       | 1          | 1           | 2          | 3                 | 0                                                              | 0          |
|                             | Bladder outlet obstruction                | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |

|          |                                        | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|----------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                        | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                     | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Bladder pain                           | 7                                                                       | 9          | 15          | 39         | 48                | 0                                                              | 0          |
|          | Bladder perforation                    | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Bladder prolapse                       | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Bladder spasm                          | 0                                                                       | 0          | 0           | 8          | 8                 | 0                                                              | 0          |
|          | Bladder stenosis                       | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Calculus bladder                       | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Calculus urinary                       | 2                                                                       | 2          | 0           | 1          | 3                 | 0                                                              | 0          |
|          | Choluria                               | 1                                                                       | 2          | 1           | 2          | 4                 | 0                                                              | 0          |
|          | Chromaturia                            | 37                                                                      | 70         | 72          | 229        | 299               | 0                                                              | 0          |
|          | Chronic kidney disease                 | 53                                                                      | 69         | 1           | 1          | 70                | 0                                                              | 0          |
|          | Costovertebral angle tenderness        | 0                                                                       | 0          | 1           | 4          | 4                 | 0                                                              | 0          |
|          | Cystitis haemorrhagic                  | 3                                                                       | 7          | 0           | 0          | 7                 | 0                                                              | 0          |
|          | Cystitis interstitial                  | 1                                                                       | 2          | 4           | 9          | 11                | 0                                                              | 0          |
|          | Cystitis noninfective                  | 4                                                                       | 4          | 27          | 31         | 35                | 0                                                              | 0          |
|          | Cystitis-like symptom                  | 0                                                                       | 0          | 2           | 4          | 4                 | 0                                                              | 0          |
|          | Diabetic nephropathy                   | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Dysuria                                | 40                                                                      | 75         | 81          | 220        | 295               | 0                                                              | 0          |
|          | End stage renal disease                | 18                                                                      | 23         | 0           | 0          | 23                | 0                                                              | 0          |
|          | Focal segmental glomerulosclerosis     | 2                                                                       | 2          | 1           | 1          | 3                 | 0                                                              | 0          |
|          | Foetal renal impairment                | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Genitourinary symptom                  | 2                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Glomerulonephritis                     | 10                                                                      | 16         | 0           | 0          | 16                | 0                                                              | 0          |
|          | Glomerulonephritis acute               | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Glomerulonephritis membranous          | 6                                                                       | 7          | 1           | 1          | 8                 | 0                                                              | 0          |
|          | Glomerulonephritis minimal lesion      | 11                                                                      | 12         | 0           | 0          | 12                | 0                                                              | 0          |
|          | Glomerulonephritis rapidly progressive | 6                                                                       | 8          | 0           | 0          | 8                 | 0                                                              | 0          |
|          | Glomerulonephropathy                   | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Goodpasture's syndrome                 | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Haematuria                             | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Haematuria                             | 60                                                                      | 85         | 82          | 175        | 260               | 0                                                              | 0          |
|          | Haemoglobinuria                        | 4                                                                       | 6          | 0           | 0          | 6                 | 0                                                              | 0          |
|          | Haemorrhage urinary tract              | 15                                                                      | 46         | 6           | 9          | 55                | 0                                                              | 0          |
|          | Hydronephrosis                         | 8                                                                       | 19         | 0           | 1          | 20                | 0                                                              | 0          |
|          | Hydroureter                            | 1                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Hypertonic bladder                     | 2                                                                       | 2          | 5           | 8          | 10                | 0                                                              | 0          |
|          | IgA nephropathy                        | 24                                                                      | 33         | 2           | 2          | 35                | 0                                                              | 0          |
|          | Incontinence                           | 27                                                                      | 43         | 31          | 112        | 155               | 0                                                              | 0          |
|          | Ketonuria                              | 0                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Kidney enlargement                     | 1                                                                       | 1          | 1           | 2          | 3                 | 0                                                              | 0          |
|          | Kidney fibrosis                        | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Kidney small                           | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Leukocyturia                           | 0                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Loss of bladder sensation              | 2                                                                       | 2          | 0           | 3          | 5                 | 0                                                              | 0          |
|          | Lower urinary tract symptoms           | 0                                                                       | 1          | 1           | 3          | 4                 | 0                                                              | 0          |
|          | Lupus nephritis                        | 2                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Microalbuminuria                       | 2                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Micturition disorder                   | 2                                                                       | 4          | 5           | 13         | 17                | 0                                                              | 0          |
|          | Micturition urgency                    | 18                                                                      | 26         | 35          | 88         | 114               | 0                                                              | 0          |
|          | Nephritic syndrome                     | 0                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |

|          |                                      | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|--------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                      | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                   | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Nephritis                            | 18                                                                      | 20         | 0           | 0          | 20                | 0                                                              | 0          |
|          | Nephrocalcinosis                     | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Nephrolithiasis                      | 47                                                                      | 101        | 5           | 11         | 112               | 0                                                              | 0          |
|          | Nephropathy                          | 5                                                                       | 9          | 1           | 1          | 10                | 0                                                              | 0          |
|          | Nephrotic syndrome                   | 20                                                                      | 27         | 1           | 1          | 28                | 0                                                              | 0          |
|          | Neurogenic bladder                   | 3                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Nocturia                             | 3                                                                       | 3          | 11          | 21         | 24                | 0                                                              | 0          |
|          | Oedematous kidney                    | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Oliguria                             | 9                                                                       | 16         | 1           | 5          | 21                | 0                                                              | 0          |
|          | Paroxysmal nocturnal haemoglobinuria | 1                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Pelvi-ureteric obstruction           | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Perinephric oedema                   | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Pollakiuria                          | 65                                                                      | 83         | 92          | 309        | 392               | 0                                                              | 0          |
|          | Polyuria                             | 25                                                                      | 44         | 33          | 56         | 100               | 0                                                              | 0          |
|          | Post infection glomerulonephritis    | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Post micturition dribble             | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Prerenal failure                     | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Proteinuria                          | 14                                                                      | 19         | 22          | 30         | 49                | 0                                                              | 0          |
|          | Pulmonary renal syndrome             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Pyelocaliectasis                     | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Renal arteriosclerosis               | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Renal artery arteriosclerosis        | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Renal artery dissection              | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Renal artery occlusion               | 2                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Renal artery stenosis                | 1                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Renal artery thrombosis              | 1                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Renal atrophy                        | 5                                                                       | 8          | 0           | 0          | 8                 | 0                                                              | 0          |
|          | Renal colic                          | 7                                                                       | 10         | 5           | 7          | 17                | 0                                                              | 0          |
|          | Renal cyst                           | 10                                                                      | 19         | 3           | 6          | 25                | 0                                                              | 0          |
|          | Renal cyst haemorrhage               | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Renal disorder                       | 15                                                                      | 37         | 27          | 39         | 76                | 0                                                              | 0          |
|          | Renal embolism                       | 0                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Renal failure                        | 101                                                                     | 197        | 1           | 2          | 199               | 0                                                              | 0          |
|          | Renal haemorrhage                    | 1                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Renal impairment                     | 85                                                                      | 120        | 6           | 8          | 128               | 0                                                              | 0          |
|          | Renal infarct                        | 18                                                                      | 28         | 0           | 0          | 28                | 0                                                              | 0          |
|          | Renal injury                         | 1                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Renal ischaemia                      | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Renal mass                           | 0                                                                       | 3          | 0           | 1          | 4                 | 0                                                              | 0          |
|          | Renal necrosis                       | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Renal pain                           | 103                                                                     | 115        | 167         | 353        | 468               | 0                                                              | 0          |
|          | Renal tubular disorder               | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Renal tubular injury                 | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Renal tubular necrosis               | 6                                                                       | 10         | 0           | 0          | 10                | 0                                                              | 0          |
|          | Renal vascular thrombosis            | 3                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Renal vasculitis                     | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Renal vein embolism                  | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Renal vein thrombosis                | 4                                                                       | 6          | 0           | 0          | 6                 | 0                                                              | 0          |
|          | Single functional kidney             | 2                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |



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|------------------------------------------|------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|                                          |                              | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM                                 | PT                           | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|                                          | Strangury                    | 0                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|                                          | Stress urinary incontinence  | 0                                                                       | 0          | 2           | 4          | 4                 | 0                                                              | 0          |
|                                          | Subcapsular renal haematoma  | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                          | Tubulointerstitial nephritis | 8                                                                       | 10         | 0           | 0          | 10                | 0                                                              | 0          |
|                                          | Ureteric dilatation          | 2                                                                       | 2          | 1           | 1          | 3                 | 0                                                              | 0          |
|                                          | Ureteric obstruction         | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                          | Ureteric stenosis            | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                          | Ureterolithiasis             | 4                                                                       | 5          | 0           | 1          | 6                 | 0                                                              | 0          |
|                                          | Urethral caruncle            | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|                                          | Urethral haemorrhage         | 1                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|                                          | Urethral pain                | 3                                                                       | 4          | 0           | 3          | 7                 | 0                                                              | 0          |
|                                          | Urethral stenosis            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                          | Urethral ulcer               | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|                                          | Urethritis noninfective      | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|                                          | Urge incontinence            | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|                                          | Urinary bladder haemorrhage  | 3                                                                       | 8          | 0           | 0          | 8                 | 0                                                              | 0          |
|                                          | Urinary hesitation           | 3                                                                       | 3          | 4           | 8          | 11                | 0                                                              | 0          |
|                                          | Urinary incontinence         | 63                                                                      | 100        | 62          | 276        | 376               | 0                                                              | 0          |
|                                          | Urinary retention            | 47                                                                      | 100        | 7           | 10         | 110               | 0                                                              | 0          |
|                                          | Urinary straining            | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                                          | Urinary tract discomfort     | 0                                                                       | 0          | 1           | 5          | 5                 | 0                                                              | 0          |
|                                          | Urinary tract disorder       | 3                                                                       | 3          | 4           | 8          | 11                | 0                                                              | 0          |
|                                          | Urinary tract inflammation   | 2                                                                       | 2          | 3           | 3          | 5                 | 0                                                              | 0          |
|                                          | Urinary tract obstruction    | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                          | Urinary tract pain           | 1                                                                       | 1          | 2           | 6          | 7                 | 0                                                              | 0          |
|                                          | Urine abnormality            | 10                                                                      | 15         | 11          | 40         | 55                | 0                                                              | 0          |
|                                          | Urine flow decreased         | 1                                                                       | 2          | 3           | 4          | 6                 | 0                                                              | 0          |
|                                          | Urine odour abnormal         | 5                                                                       | 5          | 8           | 44         | 49                | 0                                                              | 0          |
|                                          | Urogenital haemorrhage       | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                          | Vesicoureteric reflux        | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
| Reproductive system and breast disorders | *** SOC TOTAL ***            | 2895                                                                    | 3529       | 13227       | 16552      | 20081             | 0                                                              | 0          |
|                                          | Abnormal uterine bleeding    | 11                                                                      | 14         | 11          | 14         | 28                | 0                                                              | 0          |
|                                          | Abnormal withdrawal bleeding | 0                                                                       | 0          | 23          | 23         | 23                | 0                                                              | 0          |
|                                          | Adenomyosis                  | 4                                                                       | 4          | 3           | 3          | 7                 | 0                                                              | 0          |
|                                          | Adnexa uteri mass            | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|                                          | Adnexa uteri pain            | 22                                                                      | 28         | 67          | 83         | 111               | 0                                                              | 0          |
|                                          | Adnexal torsion              | 1                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|                                          | Amenorrhoea                  | 103                                                                     | 113        | 1094        | 1151       | 1264              | 0                                                              | 0          |
|                                          | Anisomastia                  | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|                                          | Atrophic vulvovaginitis      | 1                                                                       | 1          | 2           | 2          | 3                 | 0                                                              | 0          |
|                                          | Balanoposthitis              | 0                                                                       | 1          | 1           | 2          | 3                 | 0                                                              | 0          |
|                                          | Bartholin's cyst             | 0                                                                       | 0          | 1           | 3          | 3                 | 0                                                              | 0          |
|                                          | Benign prostatic hyperplasia | 4                                                                       | 7          | 1           | 2          | 9                 | 0                                                              | 0          |
|                                          | Breast atrophy               | 0                                                                       | 0          | 2           | 2          | 2                 | 0                                                              | 0          |
|                                          | Breast cyst                  | 6                                                                       | 8          | 9           | 18         | 26                | 0                                                              | 0          |
|                                          | Breast discharge             | 2                                                                       | 2          | 7           | 20         | 22                | 0                                                              | 0          |
|                                          | Breast discolouration        | 0                                                                       | 1          | 1           | 5          | 6                 | 0                                                              | 0          |
|                                          | Breast discomfort            | 6                                                                       | 7          | 35          | 67         | 74                | 0                                                              | 0          |
|                                          | Breast disorder              | 0                                                                       | 0          | 3           | 6          | 6                 | 0                                                              | 0          |

|          |                                    | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                    | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                 | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Breast disorder female             | 1                                                                       | 1          | 0           | 2          | 3                 | 0                                                              | 0          |
|          | Breast engorgement                 | 3                                                                       | 5          | 7           | 12         | 17                | 0                                                              | 0          |
|          | Breast enlargement                 | 6                                                                       | 7          | 28          | 40         | 47                | 0                                                              | 0          |
|          | Breast haematoma                   | 0                                                                       | 0          | 1           | 3          | 3                 | 0                                                              | 0          |
|          | Breast haemorrhage                 | 0                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Breast hyperplasia                 | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Breast induration                  | 1                                                                       | 1          | 3           | 10         | 11                | 0                                                              | 0          |
|          | Breast inflammation                | 3                                                                       | 3          | 19          | 31         | 34                | 0                                                              | 0          |
|          | Breast mass                        | 24                                                                      | 30         | 30          | 78         | 108               | 0                                                              | 0          |
|          | Breast milk discolouration         | 0                                                                       | 0          | 0           | 3          | 3                 | 0                                                              | 0          |
|          | Breast oedema                      | 3                                                                       | 6          | 4           | 11         | 17                | 0                                                              | 0          |
|          | Breast pain                        | 126                                                                     | 146        | 362         | 777        | 923               | 0                                                              | 0          |
|          | Breast swelling                    | 21                                                                      | 23         | 92          | 218        | 241               | 0                                                              | 0          |
|          | Breast tenderness                  | 16                                                                      | 17         | 59          | 152        | 169               | 0                                                              | 0          |
|          | Cervical cyst                      | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Cervical discharge                 | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Cervical dysplasia                 | 0                                                                       | 0          | 1           | 3          | 3                 | 0                                                              | 0          |
|          | Cervical polyp                     | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Cervix disorder                    | 1                                                                       | 1          | 2           | 2          | 3                 | 0                                                              | 0          |
|          | Cervix haemorrhage uterine         | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Cervix inflammation                | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Coital bleeding                    | 0                                                                       | 0          | 2           | 2          | 2                 | 0                                                              | 0          |
|          | Dysmenorrhoea                      | 294                                                                     | 354        | 942         | 1093       | 1447              | 0                                                              | 0          |
|          | Dyspareunia                        | 0                                                                       | 0          | 4           | 4          | 4                 | 0                                                              | 0          |
|          | Ectropion of cervix                | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Ejaculation delayed                | 2                                                                       | 2          | 0           | 1          | 3                 | 0                                                              | 0          |
|          | Ejaculation disorder               | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Ejaculation failure                | 1                                                                       | 1          | 1           | 2          | 3                 | 0                                                              | 0          |
|          | Endometrial atrophy                | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Endometrial disorder               | 4                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Endometrial hyperplasia            | 1                                                                       | 1          | 1           | 2          | 3                 | 0                                                              | 0          |
|          | Endometrial thickening             | 1                                                                       | 1          | 1           | 2          | 3                 | 0                                                              | 0          |
|          | Endometriosis                      | 15                                                                      | 18         | 13          | 17         | 35                | 0                                                              | 0          |
|          | Epididymal cyst                    | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Erectile dysfunction               | 46                                                                      | 69         | 23          | 25         | 94                | 0                                                              | 0          |
|          | Erection increased                 | 1                                                                       | 1          | 2           | 4          | 5                 | 0                                                              | 0          |
|          | Fallopian tube cyst                | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Fallopian tube disorder            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Female reproductive tract disorder | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Female sexual dysfunction          | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Feminisation acquired              | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Fibrocystic breast disease         | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Galactorrhoea                      | 1                                                                       | 1          | 6           | 9          | 10                | 0                                                              | 0          |
|          | Galactostasis                      | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Genital blister                    | 1                                                                       | 1          | 3           | 7          | 8                 | 0                                                              | 0          |
|          | Genital burning sensation          | 1                                                                       | 2          | 4           | 7          | 9                 | 0                                                              | 0          |
|          | Genital discharge                  | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Genital discolouration             | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Genital discomfort                 | 1                                                                       | 1          | 4           | 8          | 9                 | 0                                                              | 0          |

|          |                               | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|-------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                               | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                            | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Genital disorder              | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Genital erythema              | 0                                                                       | 0          | 1           | 3          | 3                 | 0                                                              | 0          |
|          | Genital haemorrhage           | 10                                                                      | 14         | 3           | 4          | 18                | 0                                                              | 0          |
|          | Genital hypoaesthesia         | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Genital lesion                | 1                                                                       | 1          | 0           | 3          | 4                 | 0                                                              | 0          |
|          | Genital odour                 | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Genital pain                  | 3                                                                       | 3          | 14          | 23         | 26                | 0                                                              | 0          |
|          | Genital paraesthesia          | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Genital rash                  | 2                                                                       | 2          | 3           | 15         | 17                | 0                                                              | 0          |
|          | Genital swelling              | 0                                                                       | 0          | 0           | 4          | 4                 | 0                                                              | 0          |
|          | Genital tract inflammation    | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Genital ulceration            | 4                                                                       | 4          | 4           | 10         | 14                | 0                                                              | 0          |
|          | Genitals enlarged             | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Gynaecomastia                 | 1                                                                       | 1          | 2           | 6          | 7                 | 0                                                              | 0          |
|          | Haematosalpinx                | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Haematospermia                | 3                                                                       | 3          | 2           | 4          | 7                 | 0                                                              | 0          |
|          | Haemorrhagic ovarian cyst     | 2                                                                       | 3          | 0           | 1          | 4                 | 0                                                              | 0          |
|          | Heavy menstrual bleeding      | 541                                                                     | 667        | 2301        | 2750       | 3417              | 0                                                              | 0          |
|          | Hydrometra                    | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Hypomenorrhoea                | 26                                                                      | 30         | 179         | 213        | 243               | 0                                                              | 0          |
|          | Infertility                   | 2                                                                       | 2          | 2           | 4          | 6                 | 0                                                              | 0          |
|          | Infertility female            | 1                                                                       | 1          | 3           | 3          | 4                 | 0                                                              | 0          |
|          | Intermenstrual bleeding       | 143                                                                     | 162        | 1166        | 1334       | 1496              | 0                                                              | 0          |
|          | Labia enlarged                | 0                                                                       | 0          | 0           | 4          | 4                 | 0                                                              | 0          |
|          | Lactation disorder            | 1                                                                       | 1          | 16          | 27         | 28                | 0                                                              | 0          |
|          | Lactation puerperal increased | 1                                                                       | 3          | 2           | 3          | 6                 | 0                                                              | 0          |
|          | Mammary duct ectasia          | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|          | Menometrorrhagia              | 12                                                                      | 14         | 70          | 76         | 90                | 0                                                              | 0          |
|          | Menopausal disorder           | 0                                                                       | 0          | 2           | 2          | 2                 | 0                                                              | 0          |
|          | Menopausal symptoms           | 2                                                                       | 3          | 27          | 30         | 33                | 0                                                              | 0          |
|          | Menopause delayed             | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Menstrual discomfort          | 4                                                                       | 5          | 99          | 105        | 110               | 0                                                              | 0          |
|          | Menstrual disorder            | 211                                                                     | 246        | 1786        | 2026       | 2272              | 0                                                              | 0          |
|          | Menstruation delayed          | 192                                                                     | 234        | 1077        | 1306       | 1540              | 0                                                              | 0          |
|          | Menstruation irregular        | 219                                                                     | 265        | 1232        | 1549       | 1814              | 0                                                              | 0          |
|          | Metrorrhoea                   | 0                                                                       | 0          | 2           | 2          | 2                 | 0                                                              | 0          |
|          | Nipple disorder               | 0                                                                       | 0          | 2           | 2          | 2                 | 0                                                              | 0          |
|          | Nipple exudate bloody         | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Nipple inflammation           | 0                                                                       | 0          | 3           | 8          | 8                 | 0                                                              | 0          |
|          | Nipple oedema                 | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Nipple pain                   | 4                                                                       | 4          | 31          | 43         | 47                | 0                                                              | 0          |
|          | Nipple swelling               | 0                                                                       | 0          | 3           | 8          | 8                 | 0                                                              | 0          |
|          | Nocturnal emission            | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Noninfective oophoritis       | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Oedema genital                | 0                                                                       | 0          | 2           | 2          | 2                 | 0                                                              | 0          |
|          | Oligomenorrhoea               | 25                                                                      | 29         | 324         | 358        | 387               | 0                                                              | 0          |
|          | Orchitis noninfective         | 0                                                                       | 0          | 2           | 2          | 2                 | 0                                                              | 0          |
|          | Organic erectile dysfunction  | 4                                                                       | 5          | 6           | 6          | 11                | 0                                                              | 0          |
|          | Ovarian cyst                  | 10                                                                      | 14         | 20          | 21         | 35                | 0                                                              | 0          |

|          |                                 | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|---------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                 | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                              | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Ovarian cyst ruptured           | 3                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Ovarian disorder                | 1                                                                       | 2          | 5           | 5          | 7                 | 0                                                              | 0          |
|          | Ovarian enlargement             | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Ovarian failure                 | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Ovarian mass                    | 3                                                                       | 4          | 2           | 2          | 6                 | 0                                                              | 0          |
|          | Ovarian necrosis                | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Ovarian vein thrombosis         | 3                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Ovulation disorder              | 1                                                                       | 1          | 6           | 9          | 10                | 0                                                              | 0          |
|          | Ovulation pain                  | 8                                                                       | 9          | 31          | 35         | 44                | 0                                                              | 0          |
|          | Painful ejaculation             | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Painful erection                | 0                                                                       | 0          | 2           | 3          | 3                 | 0                                                              | 0          |
|          | Pelvic congestion               | 0                                                                       | 0          | 3           | 3          | 3                 | 0                                                              | 0          |
|          | Pelvic discomfort               | 1                                                                       | 1          | 3           | 5          | 6                 | 0                                                              | 0          |
|          | Pelvic haematoma                | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Pelvic haemorrhage              | 2                                                                       | 3          | 1           | 1          | 4                 | 0                                                              | 0          |
|          | Pelvic organ prolapse           | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Pelvic pain                     | 35                                                                      | 46         | 76          | 146        | 192               | 0                                                              | 0          |
|          | Penile burning sensation        | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Penile discomfort               | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|          | Penile erythema                 | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Penile haemorrhage              | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Penile oedema                   | 0                                                                       | 0          | 0           | 3          | 3                 | 0                                                              | 0          |
|          | Penile pain                     | 2                                                                       | 2          | 3           | 5          | 7                 | 0                                                              | 0          |
|          | Penile rash                     | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Penile swelling                 | 0                                                                       | 1          | 3           | 4          | 5                 | 0                                                              | 0          |
|          | Penile vein thrombosis          | 1                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Penis disorder                  | 1                                                                       | 2          | 1           | 3          | 5                 | 0                                                              | 0          |
|          | Perineal cyst                   | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Perineal disorder               | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Perineal haematoma              | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Perineal pain                   | 3                                                                       | 3          | 3           | 4          | 7                 | 0                                                              | 0          |
|          | Peyronie's disease              | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Plasma cell mastitis            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Polycystic ovaries              | 4                                                                       | 4          | 9           | 10         | 14                | 0                                                              | 0          |
|          | Polymenorrhagia                 | 0                                                                       | 0          | 3           | 3          | 3                 | 0                                                              | 0          |
|          | Polymenorrhoea                  | 101                                                                     | 112        | 908         | 984        | 1096              | 0                                                              | 0          |
|          | Postmenopausal haemorrhage      | 179                                                                     | 241        | 49          | 66         | 307               | 0                                                              | 0          |
|          | Premature menopause             | 4                                                                       | 4          | 0           | 4          | 8                 | 0                                                              | 0          |
|          | Premature ovulation             | 0                                                                       | 1          | 2           | 2          | 3                 | 0                                                              | 0          |
|          | Premenstrual dysphoric disorder | 1                                                                       | 1          | 7           | 7          | 8                 | 0                                                              | 0          |
|          | Premenstrual headache           | 0                                                                       | 0          | 2           | 3          | 3                 | 0                                                              | 0          |
|          | Premenstrual pain               | 15                                                                      | 16         | 70          | 77         | 93                | 0                                                              | 0          |
|          | Premenstrual syndrome           | 17                                                                      | 20         | 63          | 79         | 99                | 0                                                              | 0          |
|          | Priapism                        | 1                                                                       | 2          | 0           | 1          | 3                 | 0                                                              | 0          |
|          | Prostatic calcification         | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Prostatic disorder              | 1                                                                       | 2          | 3           | 3          | 5                 | 0                                                              | 0          |
|          | Prostatic pain                  | 0                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Prostatitis                     | 11                                                                      | 12         | 5           | 10         | 22                | 0                                                              | 0          |
|          | Prostatomegaly                  | 1                                                                       | 2          | 1           | 11         | 13                | 0                                                              | 0          |

|          |                             | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|-----------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                             | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                          | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Pruritus genital            | 2                                                                       | 2          | 2           | 14         | 16                | 0                                                              | 0          |
|          | Retracted nipple            | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Retrograde ejaculation      | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Retrograde menstruation     | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Scrotal oedema              | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Scrotal pain                | 9                                                                       | 9          | 2           | 4          | 13                | 0                                                              | 0          |
|          | Scrotal swelling            | 1                                                                       | 1          | 1           | 5          | 6                 | 0                                                              | 0          |
|          | Scrotal ulcer               | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Semen discolouration        | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Sexual dysfunction          | 3                                                                       | 5          | 4           | 9          | 14                | 0                                                              | 0          |
|          | Shortened cervix            | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Spermatic cord inflammation | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Spermatorrhoea              | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Spontaneous ejaculation     | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Spontaneous penile erection | 0                                                                       | 0          | 2           | 4          | 4                 | 0                                                              | 0          |
|          | Superovulation              | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Suppressed lactation        | 7                                                                       | 7          | 48          | 72         | 79                | 0                                                              | 0          |
|          | Teratospermia               | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Testicular cyst             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Testicular disorder         | 1                                                                       | 1          | 1           | 2          | 3                 | 0                                                              | 0          |
|          | Testicular mass             | 1                                                                       | 1          | 0           | 2          | 3                 | 0                                                              | 0          |
|          | Testicular pain             | 18                                                                      | 23         | 26          | 63         | 86                | 0                                                              | 0          |
|          | Testicular swelling         | 9                                                                       | 10         | 8           | 21         | 31                | 0                                                              | 0          |
|          | Testis discomfort           | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|          | Uterine cervix hyperplasia  | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Uterine cervix stenosis     | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Uterine cyst                | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Uterine disorder            | 0                                                                       | 0          | 3           | 3          | 3                 | 0                                                              | 0          |
|          | Uterine enlargement         | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Uterine haemorrhage         | 21                                                                      | 29         | 7           | 8          | 37                | 0                                                              | 0          |
|          | Uterine inflammation        | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Uterine mass                | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Uterine pain                | 10                                                                      | 10         | 29          | 36         | 46                | 0                                                              | 0          |
|          | Uterine polyp               | 3                                                                       | 3          | 4           | 5          | 8                 | 0                                                              | 0          |
|          | Uterine prolapse            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Uterine spasm               | 7                                                                       | 8          | 21          | 35         | 43                | 0                                                              | 0          |
|          | Uterine tenderness          | 0                                                                       | 0          | 2           | 2          | 2                 | 0                                                              | 0          |
|          | Vaginal cyst                | 0                                                                       | 1          | 2           | 2          | 3                 | 0                                                              | 0          |
|          | Vaginal discharge           | 14                                                                      | 15         | 41          | 55         | 70                | 0                                                              | 0          |
|          | Vaginal disorder            | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Vaginal fistula             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Vaginal haemorrhage         | 161                                                                     | 206        | 418         | 635        | 841               | 0                                                              | 0          |
|          | Vaginal lesion              | 0                                                                       | 0          | 2           | 5          | 5                 | 0                                                              | 0          |
|          | Vaginal mucosal blistering  | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|          | Vaginal odour               | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Vaginal oedema              | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Vaginal prolapse            | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Vaginal ulceration          | 2                                                                       | 3          | 2           | 8          | 11                | 0                                                              | 0          |
|          | Varicocele                  | 4                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |

|                                                 |                                     | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|-------------------------------------------------|-------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|                                                 |                                     | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM                                        | PT                                  | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|                                                 | Varicose veins pelvic               | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                                 | Vulva cyst                          | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|                                                 | Vulval disorder                     | 0                                                                       | 0          | 3           | 6          | 6                 | 0                                                              | 0          |
|                                                 | Vulval haemorrhage                  | 6                                                                       | 8          | 2           | 2          | 10                | 0                                                              | 0          |
|                                                 | Vulval ulceration                   | 2                                                                       | 2          | 5           | 7          | 9                 | 0                                                              | 0          |
|                                                 | Vulvovaginal burning sensation      | 3                                                                       | 5          | 3           | 14         | 19                | 0                                                              | 0          |
|                                                 | Vulvovaginal discomfort             | 2                                                                       | 3          | 7           | 16         | 19                | 0                                                              | 0          |
|                                                 | Vulvovaginal dryness                | 3                                                                       | 3          | 4           | 7          | 10                | 0                                                              | 0          |
|                                                 | Vulvovaginal erythema               | 0                                                                       | 0          | 1           | 3          | 3                 | 0                                                              | 0          |
|                                                 | Vulvovaginal inflammation           | 0                                                                       | 0          | 2           | 3          | 3                 | 0                                                              | 0          |
|                                                 | Vulvovaginal pain                   | 8                                                                       | 9          | 12          | 27         | 36                | 0                                                              | 0          |
|                                                 | Vulvovaginal pruritus               | 2                                                                       | 3          | 11          | 31         | 34                | 0                                                              | 0          |
|                                                 | Vulvovaginal rash                   | 0                                                                       | 0          | 0           | 6          | 6                 | 0                                                              | 0          |
|                                                 | Vulvovaginal swelling               | 1                                                                       | 2          | 2           | 11         | 13                | 0                                                              | 0          |
|                                                 | Vulvovaginal ulceration             | 0                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|                                                 | Withdrawal bleed                    | 0                                                                       | 0          | 1           | 3          | 3                 | 0                                                              | 0          |
| Respiratory, thoracic and mediastinal disorders | *** SOC TOTAL ***                   | 13277                                                                   | 20630      | 13337       | 41074      | 61704             | 0                                                              | 3          |
|                                                 | Acquired diaphragmatic eventration  | 7                                                                       | 9          | 0           | 0          | 9                 | 0                                                              | 0          |
|                                                 | Acute chest syndrome                | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                                 | Acute interstitial pneumonitis      | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                                                 | Acute lung injury                   | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                                 | Acute pulmonary oedema              | 15                                                                      | 25         | 0           | 0          | 25                | 0                                                              | 0          |
|                                                 | Acute respiratory distress syndrome | 45                                                                      | 80         | 0           | 0          | 80                | 0                                                              | 0          |
|                                                 | Acute respiratory failure           | 389                                                                     | 512        | 0           | 0          | 512               | 0                                                              | 0          |
|                                                 | Adenoidal disorder                  | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|                                                 | Adenoidal hypertrophy               | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                                 | Agonal respiration                  | 5                                                                       | 11         | 0           | 0          | 11                | 0                                                              | 0          |
|                                                 | Allergic bronchitis                 | 0                                                                       | 1          | 1           | 2          | 3                 | 0                                                              | 0          |
|                                                 | Allergic cough                      | 2                                                                       | 3          | 2           | 6          | 9                 | 0                                                              | 0          |
|                                                 | Allergic respiratory disease        | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|                                                 | Allergic respiratory symptom        | 0                                                                       | 0          | 2           | 5          | 5                 | 0                                                              | 0          |
|                                                 | Allergic sinusitis                  | 0                                                                       | 0          | 1           | 5          | 5                 | 0                                                              | 0          |
|                                                 | Alveolitis                          | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                                 | Anoxia                              | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                                                 | Aphonia                             | 23                                                                      | 41         | 62          | 192        | 233               | 0                                                              | 0          |
|                                                 | Apnoea                              | 16                                                                      | 29         | 1           | 2          | 31                | 0                                                              | 0          |
|                                                 | Apnoeic attack                      | 1                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|                                                 | Asphyxia                            | 5                                                                       | 16         | 0           | 1          | 17                | 0                                                              | 0          |
|                                                 | Aspiration                          | 23                                                                      | 53         | 0           | 1          | 54                | 0                                                              | 0          |
|                                                 | Asthma                              | 182                                                                     | 245        | 207         | 580        | 825               | 0                                                              | 0          |
|                                                 | Asthma exercise induced             | 1                                                                       | 1          | 3           | 4          | 5                 | 0                                                              | 0          |
|                                                 | Asthma late onset                   | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                                 | Asthmatic crisis                    | 23                                                                      | 25         | 5           | 6          | 31                | 0                                                              | 0          |
|                                                 | Atelectasis                         | 88                                                                      | 141        | 9           | 19         | 160               | 0                                                              | 0          |
|                                                 | Autoimmune lung disease             | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                                 | Bradypnoea                          | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                                 | Brief resolved unexplained event    | 2                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|                                                 | Bronchial disorder                  | 0                                                                       | 0          | 3           | 5          | 5                 | 0                                                              | 0          |
|                                                 | Bronchial haemorrhage               | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |

|          |                                            | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|--------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                            | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                         | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Bronchial hyperreactivity                  | 3                                                                       | 6          | 2           | 7          | 13                | 0                                                              | 0          |
|          | Bronchial irritation                       | 4                                                                       | 5          | 0           | 1          | 6                 | 0                                                              | 0          |
|          | Bronchial obstruction                      | 2                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Bronchial oedema                           | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Bronchial secretion retention              | 1                                                                       | 2          | 1           | 2          | 4                 | 0                                                              | 0          |
|          | Bronchial wall thickening                  | 10                                                                      | 11         | 0           | 0          | 11                | 0                                                              | 0          |
|          | Bronchiectasis                             | 10                                                                      | 15         | 0           | 0          | 15                | 0                                                              | 0          |
|          | Bronchiolitis obliterans syndrome          | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Bronchitis chronic                         | 1                                                                       | 1          | 0           | 4          | 5                 | 0                                                              | 0          |
|          | Bronchopleural fistula                     | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Bronchopneumopathy                         | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Bronchospasm                               | 25                                                                      | 42         | 39          | 96         | 138               | 0                                                              | 0          |
|          | Bronchostenosis                            | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Catarrh                                    | 5                                                                       | 7          | 11          | 17         | 24                | 0                                                              | 0          |
|          | Cheyne-Stokes respiration                  | 0                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Childhood asthma                           | 2                                                                       | 2          | 0           | 3          | 5                 | 0                                                              | 0          |
|          | Choking                                    | 31                                                                      | 71         | 1           | 7          | 78                | 0                                                              | 0          |
|          | Choking sensation                          | 7                                                                       | 15         | 21          | 53         | 68                | 0                                                              | 0          |
|          | Chronic obstructive pulmonary disease      | 79                                                                      | 139        | 16          | 51         | 190               | 0                                                              | 0          |
|          | Chronic respiratory disease                | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Chronic respiratory failure                | 7                                                                       | 10         | 0           | 0          | 10                | 0                                                              | 0          |
|          | Confirmed e-cigarette or vaping product us | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Cough                                      | 1589                                                                    | 2056       | 2494        | 6616       | 8672              | 0                                                              | 1          |
|          | Cough decreased                            | 0                                                                       | 0          | 0           | 5          | 5                 | 0                                                              | 0          |
|          | Cough variant asthma                       | 1                                                                       | 1          | 0           | 3          | 4                 | 0                                                              | 0          |
|          | Cystic lung disease                        | 2                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Dependence on respirator                   | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Diaphragm muscle weakness                  | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Diaphragmalgia                             | 5                                                                       | 7          | 6           | 14         | 21                | 0                                                              | 0          |
|          | Diaphragmatic disorder                     | 3                                                                       | 3          | 1           | 1          | 4                 | 0                                                              | 0          |
|          | Diaphragmatic paralysis                    | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Diaphragmatic spasm                        | 3                                                                       | 3          | 0           | 1          | 4                 | 0                                                              | 0          |
|          | Diffuse alveolar damage                    | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Dry throat                                 | 18                                                                      | 34         | 61          | 278        | 312               | 0                                                              | 0          |
|          | Dysphonia                                  | 60                                                                      | 120        | 198         | 649        | 769               | 0                                                              | 0          |
|          | Dyspnoea                                   | 4232                                                                    | 6358       | 4121        | 11131      | 17489             | 0                                                              | 0          |
|          | Dyspnoea at rest                           | 28                                                                      | 42         | 2           | 4          | 46                | 0                                                              | 0          |
|          | Dyspnoea exertional                        | 241                                                                     | 353        | 106         | 198        | 551               | 0                                                              | 0          |
|          | Dyspnoea paroxysmal nocturnal              | 6                                                                       | 7          | 0           | 5          | 12                | 0                                                              | 0          |
|          | Ear, nose and throat disorder              | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Emphysema                                  | 16                                                                      | 24         | 4           | 9          | 33                | 0                                                              | 0          |
|          | Eosinophilic bronchitis                    | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Eosinophilic pleural effusion              | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Eosinophilic pneumonia                     | 4                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Eosinophilic pneumonia acute               | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Eosinophilic pneumonia chronic             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Epiglottic oedema                          | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Epiglottis ulcer                           | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Epistaxis                                  | 149                                                                     | 251        | 411         | 997        | 1248              | 0                                                              | 0          |

|          |                                              | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|----------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                              | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                           | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Gaspings syndrome                            | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Grunting                                     | 0                                                                       | 2          | 2           | 7          | 9                 | 0                                                              | 0          |
|          | Haemoptysis                                  | 55                                                                      | 93         | 26          | 80         | 173               | 0                                                              | 0          |
|          | Haemothorax                                  | 0                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Hiccups                                      | 9                                                                       | 17         | 8           | 45         | 62                | 0                                                              | 0          |
|          | Hypercapnia                                  | 13                                                                      | 27         | 0           | 0          | 27                | 0                                                              | 0          |
|          | Hypersensitivity pneumonitis                 | 3                                                                       | 8          | 0           | 0          | 8                 | 0                                                              | 0          |
|          | Hyperventilation                             | 42                                                                      | 72         | 84          | 225        | 297               | 0                                                              | 0          |
|          | Hypocapnia                                   | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Hypopnoea                                    | 31                                                                      | 54         | 23          | 126        | 180               | 0                                                              | 0          |
|          | Hypoventilation                              | 3                                                                       | 5          | 2           | 2          | 7                 | 0                                                              | 0          |
|          | Hypoxia                                      | 510                                                                     | 790        | 5           | 9          | 799               | 0                                                              | 0          |
|          | Idiopathic interstitial pneumonia            | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Idiopathic pulmonary fibrosis                | 5                                                                       | 6          | 0           | 0          | 6                 | 0                                                              | 0          |
|          | Immune-mediated lung disease                 | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Increased bronchial secretion                | 2                                                                       | 6          | 7           | 11         | 17                | 0                                                              | 0          |
|          | Increased upper airway secretion             | 5                                                                       | 7          | 4           | 24         | 31                | 0                                                              | 0          |
|          | Increased viscosity of bronchial secretion   | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Increased viscosity of upper respiratory sec | 6                                                                       | 8          | 10          | 22         | 30                | 0                                                              | 0          |
|          | Infantile apnoea                             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Interstitial lung disease                    | 51                                                                      | 78         | 0           | 2          | 80                | 0                                                              | 0          |
|          | Intranasal hypoaesthesia                     | 0                                                                       | 1          | 0           | 6          | 7                 | 0                                                              | 0          |
|          | Irregular breathing                          | 4                                                                       | 5          | 6           | 21         | 26                | 0                                                              | 0          |
|          | Kussmaul respiration                         | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Laryngeal discomfort                         | 0                                                                       | 0          | 18          | 23         | 23                | 0                                                              | 0          |
|          | Laryngeal haemorrhage                        | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Laryngeal inflammation                       | 1                                                                       | 1          | 3           | 3          | 4                 | 0                                                              | 0          |
|          | Laryngeal mass                               | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|          | Laryngeal obstruction                        | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Laryngeal oedema                             | 36                                                                      | 56         | 1           | 1          | 57                | 0                                                              | 0          |
|          | Laryngeal pain                               | 2                                                                       | 2          | 1           | 2          | 4                 | 0                                                              | 0          |
|          | Laryngeal stenosis                           | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Laryngospasm                                 | 3                                                                       | 5          | 2           | 6          | 11                | 0                                                              | 0          |
|          | Larynx irritation                            | 1                                                                       | 1          | 4           | 7          | 8                 | 0                                                              | 0          |
|          | Low lung compliance                          | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Lower respiratory tract congestion           | 1                                                                       | 1          | 6           | 22         | 23                | 0                                                              | 0          |
|          | Lung consolidation                           | 38                                                                      | 56         | 4           | 4          | 60                | 0                                                              | 0          |
|          | Lung cyst                                    | 2                                                                       | 2          | 0           | 1          | 3                 | 0                                                              | 0          |
|          | Lung disorder                                | 84                                                                      | 109        | 41          | 66         | 175               | 0                                                              | 0          |
|          | Lung hyperinflation                          | 5                                                                       | 8          | 2           | 2          | 10                | 0                                                              | 0          |
|          | Lung hypoinflation                           | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Lung infiltration                            | 149                                                                     | 217        | 8           | 16         | 233               | 0                                                              | 0          |
|          | Lung opacity                                 | 240                                                                     | 321        | 10          | 14         | 335               | 0                                                              | 0          |
|          | Lupus pneumonitis                            | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Lymphangioleiomyomatosis                     | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Meconium aspiration syndrome                 | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Mediastinal disorder                         | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Mediastinal haematoma                        | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Mediastinal mass                             | 2                                                                       | 4          | 1           | 1          | 5                 | 0                                                              | 0          |



|          |                                        | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|----------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                        | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                     | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Mouth breathing                        | 3                                                                       | 3          | 2           | 7          | 10                | 0                                                              | 0          |
|          | Nasal cavity mass                      | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Nasal congestion                       | 110                                                                     | 137        | 496         | 1731       | 1868              | 0                                                              | 0          |
|          | Nasal crusting                         | 0                                                                       | 0          | 2           | 6          | 6                 | 0                                                              | 0          |
|          | Nasal discharge discolouration         | 0                                                                       | 0          | 1           | 8          | 8                 | 0                                                              | 0          |
|          | Nasal discomfort                       | 15                                                                      | 19         | 42          | 134        | 153               | 0                                                              | 0          |
|          | Nasal disorder                         | 0                                                                       | 0          | 1           | 8          | 8                 | 0                                                              | 0          |
|          | Nasal dryness                          | 4                                                                       | 4          | 12          | 52         | 56                | 0                                                              | 0          |
|          | Nasal inflammation                     | 1                                                                       | 1          | 5           | 17         | 18                | 0                                                              | 0          |
|          | Nasal mucosal blistering               | 0                                                                       | 0          | 0           | 3          | 3                 | 0                                                              | 0          |
|          | Nasal mucosal discolouration           | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Nasal mucosal disorder                 | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Nasal obstruction                      | 0                                                                       | 0          | 3           | 10         | 10                | 0                                                              | 0          |
|          | Nasal oedema                           | 4                                                                       | 5          | 9           | 28         | 33                | 0                                                              | 0          |
|          | Nasal polyps                           | 0                                                                       | 0          | 1           | 3          | 3                 | 0                                                              | 0          |
|          | Nasal pruritus                         | 1                                                                       | 2          | 6           | 27         | 29                | 0                                                              | 0          |
|          | Nasal septum deviation                 | 0                                                                       | 0          | 2           | 4          | 4                 | 0                                                              | 0          |
|          | Nasal septum disorder                  | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Nasal turbinate hypertrophy            | 0                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Nasal ulcer                            | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Neonatal aspiration                    | 0                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Neonatal dyspnoea                      | 2                                                                       | 2          | 0           | 1          | 3                 | 0                                                              | 0          |
|          | Neonatal hypoxia                       | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Neonatal respiratory distress          | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Neonatal respiratory distress syndrome | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Nocturnal dyspnoea                     | 1                                                                       | 1          | 2           | 4          | 5                 | 0                                                              | 0          |
|          | Obstructive airways disorder           | 11                                                                      | 29         | 7           | 26         | 55                | 0                                                              | 0          |
|          | Organising pneumonia                   | 8                                                                       | 13         | 0           | 0          | 13                | 0                                                              | 0          |
|          | Oropharyngeal blistering               | 8                                                                       | 20         | 2           | 2          | 22                | 0                                                              | 0          |
|          | Oropharyngeal discomfort               | 29                                                                      | 53         | 208         | 696        | 749               | 0                                                              | 0          |
|          | Oropharyngeal oedema                   | 0                                                                       | 2          | 2           | 5          | 7                 | 0                                                              | 0          |
|          | Oropharyngeal pain                     | 537                                                                     | 683        | 1438        | 4220       | 4903              | 0                                                              | 0          |
|          | Oropharyngeal plaque                   | 0                                                                       | 0          | 3           | 4          | 4                 | 0                                                              | 0          |
|          | Oropharyngeal spasm                    | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Oropharyngeal swelling                 | 1                                                                       | 1          | 8           | 13         | 14                | 0                                                              | 0          |
|          | Orthopnoea                             | 24                                                                      | 30         | 4           | 9          | 39                | 0                                                              | 0          |
|          | Painful respiration                    | 54                                                                      | 94         | 48          | 126        | 220               | 0                                                              | 0          |
|          | Paranasal cyst                         | 1                                                                       | 1          | 0           | 2          | 3                 | 0                                                              | 0          |
|          | Paranasal sinus discomfort             | 12                                                                      | 20         | 41          | 210        | 230               | 0                                                              | 0          |
|          | Paranasal sinus haemorrhage            | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|          | Paranasal sinus hypersecretion         | 1                                                                       | 2          | 5           | 18         | 20                | 0                                                              | 0          |
|          | Paranasal sinus hyposecretion          | 1                                                                       | 1          | 2           | 4          | 5                 | 0                                                              | 0          |
|          | Paranasal sinus inflammation           | 2                                                                       | 4          | 4           | 14         | 18                | 0                                                              | 0          |
|          | Pharyngeal disorder                    | 0                                                                       | 0          | 2           | 4          | 4                 | 0                                                              | 0          |
|          | Pharyngeal enanthema                   | 0                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Pharyngeal erythema                    | 3                                                                       | 6          | 15          | 58         | 64                | 0                                                              | 0          |
|          | Pharyngeal exudate                     | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Pharyngeal haemorrhage                 | 4                                                                       | 7          | 1           | 2          | 9                 | 0                                                              | 0          |
|          | Pharyngeal hypoaesthesia               | 7                                                                       | 13         | 9           | 132        | 145               | 0                                                              | 0          |

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|----------|-------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                           | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                        | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Pharyngeal inflammation                   | 2                                                                       | 2          | 7           | 7          | 9                 | 0                                                              | 0          |
|          | Pharyngeal mass                           | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Pharyngeal oedema                         | 18                                                                      | 27         | 20          | 37         | 64                | 0                                                              | 0          |
|          | Pharyngeal paraesthesia                   | 5                                                                       | 19         | 11          | 268        | 287               | 0                                                              | 0          |
|          | Pharyngeal swelling                       | 107                                                                     | 250        | 170         | 1232       | 1482              | 0                                                              | 0          |
|          | Pharyngeal ulceration                     | 1                                                                       | 1          | 1           | 8          | 9                 | 0                                                              | 0          |
|          | Pleural calcification                     | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Pleural disorder                          | 1                                                                       | 1          | 2           | 2          | 3                 | 0                                                              | 0          |
|          | Pleural effusion                          | 163                                                                     | 282        | 16          | 31         | 313               | 0                                                              | 0          |
|          | Pleural fibrosis                          | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Pleural thickening                        | 6                                                                       | 10         | 0           | 1          | 11                | 0                                                              | 0          |
|          | Pleurisy                                  | 30                                                                      | 42         | 23          | 44         | 86                | 0                                                              | 0          |
|          | Pleuritic pain                            | 42                                                                      | 74         | 21          | 38         | 112               | 0                                                              | 0          |
|          | Pneumomediastinum                         | 4                                                                       | 7          | 0           | 0          | 7                 | 0                                                              | 0          |
|          | Pneumonitis                               | 47                                                                      | 69         | 14          | 39         | 108               | 0                                                              | 1          |
|          | Pneumonitis aspiration                    | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Pneumothorax                              | 33                                                                      | 56         | 0           | 0          | 56                | 0                                                              | 0          |
|          | Pneumothorax spontaneous                  | 1                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Productive cough                          | 153                                                                     | 197        | 145         | 410        | 607               | 0                                                              | 0          |
|          | Prolonged expiration                      | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Pulmonary air leakage                     | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Pulmonary alveolar haemorrhage            | 6                                                                       | 7          | 0           | 0          | 7                 | 0                                                              | 0          |
|          | Pulmonary amyloidosis                     | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Pulmonary arterial hypertension           | 5                                                                       | 6          | 1           | 1          | 7                 | 0                                                              | 0          |
|          | Pulmonary arteriopathy                    | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Pulmonary artery dilatation               | 4                                                                       | 6          | 0           | 0          | 6                 | 0                                                              | 0          |
|          | Pulmonary artery occlusion                | 4                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Pulmonary artery stenosis                 | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Pulmonary artery thrombosis               | 6                                                                       | 9          | 0           | 0          | 9                 | 0                                                              | 0          |
|          | Pulmonary artery wall hypertrophy         | 1                                                                       | 2          | 0           | 1          | 3                 | 0                                                              | 0          |
|          | Pulmonary calcification                   | 4                                                                       | 5          | 1           | 1          | 6                 | 0                                                              | 0          |
|          | Pulmonary cavitation                      | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Pulmonary congestion                      | 59                                                                      | 155        | 5           | 17         | 172               | 0                                                              | 0          |
|          | Pulmonary embolism                        | 988                                                                     | 1999       | 9           | 10         | 2009              | 0                                                              | 1          |
|          | Pulmonary fibrosis                        | 31                                                                      | 51         | 0           | 0          | 51                | 0                                                              | 0          |
|          | Pulmonary granuloma                       | 5                                                                       | 15         | 0           | 0          | 15                | 0                                                              | 0          |
|          | Pulmonary haematoma                       | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Pulmonary haemorrhage                     | 10                                                                      | 15         | 0           | 0          | 15                | 0                                                              | 0          |
|          | Pulmonary hilar enlargement               | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Pulmonary hilum mass                      | 2                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Pulmonary hypertension                    | 32                                                                      | 54         | 0           | 0          | 54                | 0                                                              | 0          |
|          | Pulmonary infarction                      | 31                                                                      | 70         | 0           | 0          | 70                | 0                                                              | 0          |
|          | Pulmonary interstitial emphysema syndrome | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Pulmonary mass                            | 52                                                                      | 80         | 8           | 27         | 107               | 0                                                              | 0          |
|          | Pulmonary microemboli                     | 4                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Pulmonary oedema                          | 126                                                                     | 225        | 3           | 7          | 232               | 0                                                              | 0          |
|          | Pulmonary oedema neonatal                 | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Pulmonary pain                            | 48                                                                      | 64         | 95          | 220        | 284               | 0                                                              | 0          |
|          | Pulmonary sarcoidosis                     | 3                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |

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|----------|---------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                       | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                    | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Pulmonary sensitisation               | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Pulmonary thrombosis                  | 141                                                                     | 246        | 1           | 1          | 247               | 0                                                              | 0          |
|          | Pulmonary toxicity                    | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Pulmonary vascular disorder           | 5                                                                       | 8          | 1           | 1          | 9                 | 0                                                              | 0          |
|          | Pulmonary vasculitis                  | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Pulmonary venous hypertension         | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Pulmonary venous thrombosis           | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Rales                                 | 22                                                                      | 39         | 2           | 14         | 53                | 0                                                              | 0          |
|          | Reactive airways dysfunction syndrome | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Reflux laryngitis                     | 1                                                                       | 2          | 0           | 2          | 4                 | 0                                                              | 0          |
|          | Respiration abnormal                  | 41                                                                      | 63         | 37          | 110        | 173               | 0                                                              | 0          |
|          | Respiratory acidosis                  | 2                                                                       | 6          | 1           | 1          | 7                 | 0                                                              | 0          |
|          | Respiratory alkalosis                 | 1                                                                       | 3          | 0           | 1          | 4                 | 0                                                              | 0          |
|          | Respiratory arrest                    | 40                                                                      | 151        | 1           | 2          | 153               | 0                                                              | 0          |
|          | Respiratory depression                | 4                                                                       | 20         | 0           | 0          | 20                | 0                                                              | 0          |
|          | Respiratory depth decreased           | 2                                                                       | 2          | 2           | 2          | 4                 | 0                                                              | 0          |
|          | Respiratory disorder                  | 38                                                                      | 69         | 32          | 69         | 138               | 0                                                              | 0          |
|          | Respiratory disorder neonatal         | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Respiratory distress                  | 111                                                                     | 239        | 12          | 16         | 255               | 0                                                              | 0          |
|          | Respiratory failure                   | 175                                                                     | 306        | 0           | 0          | 306               | 0                                                              | 0          |
|          | Respiratory fatigue                   | 4                                                                       | 5          | 6           | 10         | 15                | 0                                                              | 0          |
|          | Respiratory gas exchange disorder     | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Respiratory muscle weakness           | 1                                                                       | 3          | 1           | 2          | 5                 | 0                                                              | 0          |
|          | Respiratory symptom                   | 38                                                                      | 44         | 24          | 45         | 89                | 0                                                              | 0          |
|          | Respiratory tract congestion          | 119                                                                     | 152        | 186         | 577        | 729               | 0                                                              | 0          |
|          | Respiratory tract haemorrhage         | 1                                                                       | 4          | 1           | 1          | 5                 | 0                                                              | 0          |
|          | Respiratory tract inflammation        | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Respiratory tract irritation          | 3                                                                       | 5          | 7           | 23         | 28                | 0                                                              | 0          |
|          | Respiratory tract oedema              | 4                                                                       | 11         | 1           | 1          | 12                | 0                                                              | 0          |
|          | Respiratory tract ulceration          | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Restrictive pulmonary disease         | 2                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Rhinalgia                             | 6                                                                       | 8          | 11          | 41         | 49                | 0                                                              | 0          |
|          | Rhinitis allergic                     | 4                                                                       | 5          | 16          | 26         | 31                | 0                                                              | 0          |
|          | Rhinorrhoea                           | 186                                                                     | 222        | 840         | 2380       | 2602              | 0                                                              | 0          |
|          | Rhonchi                               | 4                                                                       | 10         | 2           | 7          | 17                | 0                                                              | 0          |
|          | Sinonasal obstruction                 | 2                                                                       | 2          | 4           | 6          | 8                 | 0                                                              | 0          |
|          | Sinus congestion                      | 26                                                                      | 30         | 62          | 280        | 310               | 0                                                              | 0          |
|          | Sinus disorder                        | 11                                                                      | 14         | 41          | 138        | 152               | 0                                                              | 0          |
|          | Sinus pain                            | 56                                                                      | 62         | 35          | 149        | 211               | 0                                                              | 0          |
|          | Sinus polyp                           | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Sleep apnoea syndrome                 | 20                                                                      | 25         | 17          | 30         | 55                | 0                                                              | 0          |
|          | Small airways disease                 | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Sneezing                              | 46                                                                      | 51         | 235         | 687        | 738               | 0                                                              | 0          |
|          | Snoring                               | 6                                                                       | 11         | 9           | 22         | 33                | 0                                                              | 0          |
|          | Sputum discoloured                    | 32                                                                      | 42         | 13          | 28         | 70                | 0                                                              | 0          |
|          | Sputum increased                      | 4                                                                       | 6          | 5           | 5          | 11                | 0                                                              | 0          |
|          | Sputum retention                      | 0                                                                       | 1          | 2           | 2          | 3                 | 0                                                              | 0          |
|          | Status asthmaticus                    | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Stridor                               | 5                                                                       | 17         | 5           | 21         | 38                | 0                                                              | 0          |

|                                        |                                          | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------------------------------------|------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|                                        |                                          | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM                               | PT                                       | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|                                        | Suffocation feeling                      | 8                                                                       | 11         | 15          | 28         | 39                | 0                                                              | 0          |
|                                        | Tachypnoea                               | 89                                                                      | 139        | 17          | 100        | 239               | 0                                                              | 0          |
|                                        | Throat clearing                          | 3                                                                       | 12         | 11          | 111        | 123               | 0                                                              | 0          |
|                                        | Throat irritation                        | 73                                                                      | 129        | 258         | 1670       | 1799              | 0                                                              | 0          |
|                                        | Throat lesion                            | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|                                        | Throat tightness                         | 96                                                                      | 271        | 168         | 1614       | 1885              | 0                                                              | 0          |
|                                        | Tonsillar cyst                           | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                        | Tonsillar disorder                       | 0                                                                       | 0          | 3           | 6          | 6                 | 0                                                              | 0          |
|                                        | Tonsillar erythema                       | 3                                                                       | 3          | 2           | 7          | 10                | 0                                                              | 0          |
|                                        | Tonsillar haemorrhage                    | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                        | Tonsillar hypertrophy                    | 13                                                                      | 17         | 24          | 79         | 96                | 0                                                              | 0          |
|                                        | Tonsillar inflammation                   | 2                                                                       | 2          | 7           | 15         | 17                | 0                                                              | 0          |
|                                        | Tonsillar ulcer                          | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|                                        | Tonsillolith                             | 0                                                                       | 0          | 1           | 3          | 3                 | 0                                                              | 0          |
|                                        | Tracheal compression                     | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                        | Tracheal disorder                        | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                        | Tracheal diverticulum                    | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                        | Tracheal inflammation                    | 0                                                                       | 1          | 1           | 3          | 4                 | 0                                                              | 0          |
|                                        | Tracheal oedema                          | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                        | Tracheal pain                            | 2                                                                       | 2          | 3           | 5          | 7                 | 0                                                              | 0          |
|                                        | Tracheal stenosis                        | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                        | Tracheomalacia                           | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                        | Transient tachypnoea of the newborn      | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|                                        | Upper airway obstruction                 | 1                                                                       | 2          | 1           | 1          | 3                 | 0                                                              | 0          |
|                                        | Upper respiratory tract congestion       | 3                                                                       | 4          | 5           | 22         | 26                | 0                                                              | 0          |
|                                        | Upper respiratory tract inflammation     | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|                                        | Upper respiratory tract irritation       | 0                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|                                        | Upper-airway cough syndrome              | 7                                                                       | 10         | 20          | 126        | 136               | 0                                                              | 0          |
|                                        | Use of accessory respiratory muscles     | 2                                                                       | 3          | 1           | 6          | 9                 | 0                                                              | 0          |
|                                        | Vocal cord disorder                      | 2                                                                       | 3          | 5           | 5          | 8                 | 0                                                              | 0          |
|                                        | Vocal cord dysfunction                   | 4                                                                       | 5          | 1           | 5          | 10                | 0                                                              | 0          |
|                                        | Vocal cord inflammation                  | 1                                                                       | 1          | 0           | 2          | 3                 | 0                                                              | 0          |
|                                        | Vocal cord scarring                      | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|                                        | Vocal cord thickening                    | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|                                        | Wheezing                                 | 189                                                                     | 283        | 153         | 782        | 1065              | 0                                                              | 0          |
|                                        | Yawning                                  | 4                                                                       | 5          | 13          | 33         | 38                | 0                                                              | 0          |
| Skin and subcutaneous tissue disorders | *** SOC TOTAL ***                        | 7877                                                                    | 11435      | 26803       | 103740     | 115175            | 0                                                              | 0          |
|                                        | Acne                                     | 27                                                                      | 31         | 96          | 215        | 246               | 0                                                              | 0          |
|                                        | Acne cystic                              | 0                                                                       | 0          | 1           | 5          | 5                 | 0                                                              | 0          |
|                                        | Actinic keratosis                        | 0                                                                       | 0          | 0           | 4          | 4                 | 0                                                              | 0          |
|                                        | Acute cutaneous lupus erythematosus      | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                        | Acute febrile neutrophilic dermatosis    | 4                                                                       | 6          | 1           | 2          | 8                 | 0                                                              | 0          |
|                                        | Acute generalised exanthematous pustulos | 9                                                                       | 10         | 2           | 2          | 12                | 0                                                              | 0          |
|                                        | Alopecia                                 | 82                                                                      | 98         | 300         | 500        | 598               | 0                                                              | 0          |
|                                        | Alopecia areata                          | 12                                                                      | 13         | 29          | 39         | 52                | 0                                                              | 0          |
|                                        | Alopecia totalis                         | 2                                                                       | 2          | 0           | 1          | 3                 | 0                                                              | 0          |
|                                        | Alopecia universalis                     | 1                                                                       | 1          | 2           | 3          | 4                 | 0                                                              | 0          |
|                                        | Androgenetic alopecia                    | 0                                                                       | 1          | 2           | 4          | 5                 | 0                                                              | 0          |
|                                        | Angioedema                               | 238                                                                     | 635        | 38          | 50         | 685               | 0                                                              | 0          |

|          |                                            | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|--------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                            | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                         | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Anhidrosis                                 | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Autoimmune dermatitis                      | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Blister                                    | 97                                                                      | 139        | 236         | 865        | 1004              | 0                                                              | 0          |
|          | Blister rupture                            | 3                                                                       | 4          | 2           | 13         | 17                | 0                                                              | 0          |
|          | Blood blister                              | 2                                                                       | 11         | 14          | 46         | 57                | 0                                                              | 0          |
|          | Brachioradial pruritus                     | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Bromhidrosis                               | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Brow ptosis                                | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Bullous haemorrhagic dermatosis            | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Butterfly rash                             | 0                                                                       | 1          | 2           | 14         | 15                | 0                                                              | 0          |
|          | Capillaritis                               | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|          | Cellulite                                  | 0                                                                       | 0          | 4           | 5          | 5                 | 0                                                              | 0          |
|          | Chronic pigmented purpura                  | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|          | Chronic spontaneous urticaria              | 8                                                                       | 9          | 4           | 4          | 13                | 0                                                              | 0          |
|          | Circumoral oedema                          | 0                                                                       | 0          | 1           | 6          | 6                 | 0                                                              | 0          |
|          | Circumoral swelling                        | 1                                                                       | 1          | 7           | 20         | 21                | 0                                                              | 0          |
|          | Cold sweat                                 | 263                                                                     | 331        | 457         | 1447       | 1778              | 0                                                              | 0          |
|          | Cold urticaria                             | 0                                                                       | 2          | 8           | 13         | 15                | 0                                                              | 0          |
|          | Cutaneous lupus erythematosus              | 4                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Cutaneous sarcoidosis                      | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Cutaneous symptom                          | 0                                                                       | 1          | 17          | 19         | 20                | 0                                                              | 0          |
|          | Cutaneous vasculitis                       | 23                                                                      | 41         | 1           | 1          | 42                | 0                                                              | 0          |
|          | Cutis verticis gyrata                      | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Dandruff                                   | 0                                                                       | 0          | 1           | 5          | 5                 | 0                                                              | 0          |
|          | Decubitus ulcer                            | 6                                                                       | 7          | 3           | 8          | 15                | 0                                                              | 0          |
|          | Dermal cyst                                | 5                                                                       | 6          | 4           | 8          | 14                | 0                                                              | 0          |
|          | Dermatitis                                 | 33                                                                      | 42         | 66          | 203        | 245               | 0                                                              | 0          |
|          | Dermatitis acneiform                       | 3                                                                       | 4          | 16          | 56         | 60                | 0                                                              | 0          |
|          | Dermatitis allergic                        | 45                                                                      | 59         | 110         | 285        | 344               | 0                                                              | 0          |
|          | Dermatitis atopic                          | 11                                                                      | 11         | 13          | 31         | 42                | 0                                                              | 0          |
|          | Dermatitis bullous                         | 41                                                                      | 79         | 13          | 21         | 100               | 0                                                              | 0          |
|          | Dermatitis contact                         | 5                                                                       | 6          | 18          | 73         | 79                | 0                                                              | 0          |
|          | Dermatitis diaper                          | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|          | Dermatitis exfoliative generalised         | 5                                                                       | 11         | 0           | 1          | 12                | 0                                                              | 0          |
|          | Dermatitis herpetiformis                   | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Dermatitis psoriasiform                    | 0                                                                       | 0          | 2           | 8          | 8                 | 0                                                              | 0          |
|          | Dermatomyositis                            | 6                                                                       | 13         | 0           | 1          | 14                | 0                                                              | 0          |
|          | Dermatosis                                 | 0                                                                       | 0          | 6           | 8          | 8                 | 0                                                              | 0          |
|          | Diffuse alopecia                           | 0                                                                       | 0          | 9           | 11         | 11                | 0                                                              | 0          |
|          | Drug eruption                              | 13                                                                      | 14         | 33          | 43         | 57                | 0                                                              | 0          |
|          | Drug reaction with eosinophilia and system | 10                                                                      | 23         | 0           | 0          | 23                | 0                                                              | 0          |
|          | Dry skin                                   | 40                                                                      | 52         | 95          | 343        | 395               | 0                                                              | 0          |
|          | Dyshidrotic eczema                         | 4                                                                       | 8          | 11          | 19         | 27                | 0                                                              | 0          |
|          | Ecchymosis                                 | 23                                                                      | 32         | 62          | 106        | 138               | 0                                                              | 0          |
|          | Eczema                                     | 55                                                                      | 64         | 246         | 417        | 481               | 0                                                              | 0          |
|          | Eczema asteatotic                          | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|          | Eczema nummular                            | 1                                                                       | 1          | 5           | 13         | 14                | 0                                                              | 0          |
|          | Eczema vesicular                           | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Eczema weeping                             | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |

|          |                                         | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|-----------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                         | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                      | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Eosinophilic cellulitis                 | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Ephelides                               | 0                                                                       | 0          | 1           | 6          | 6                 | 0                                                              | 0          |
|          | Epidermolysis                           | 2                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Erythema                                | 602                                                                     | 914        | 3890        | 15571      | 16485             | 0                                                              | 0          |
|          | Erythema annulare                       | 0                                                                       | 0          | 7           | 15         | 15                | 0                                                              | 0          |
|          | Erythema dyschromicum perstans          | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Erythema elevatum diutinum              | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Erythema multiforme                     | 111                                                                     | 224        | 10          | 15         | 239               | 0                                                              | 0          |
|          | Erythema nodosum                        | 17                                                                      | 22         | 32          | 57         | 79                | 0                                                              | 0          |
|          | Erythrosis                              | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Excessive granulation tissue            | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|          | Exfoliative rash                        | 5                                                                       | 6          | 18          | 53         | 59                | 0                                                              | 0          |
|          | Facial wasting                          | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Fixed eruption                          | 1                                                                       | 1          | 4           | 8          | 9                 | 0                                                              | 0          |
|          | Flagellate dermatitis                   | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Fordyce spots                           | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|          | Generalised bullous fixed drug eruption | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Granuloma annulare                      | 2                                                                       | 2          | 4           | 13         | 15                | 0                                                              | 0          |
|          | Granuloma skin                          | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Granulomatous dermatitis                | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Guttate psoriasis                       | 2                                                                       | 2          | 7           | 9          | 11                | 0                                                              | 0          |
|          | Haemorrhage subcutaneous                | 12                                                                      | 21         | 0           | 0          | 21                | 0                                                              | 0          |
|          | Haemorrhage subepidermal                | 0                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Haemosiderin stain                      | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Hair colour changes                     | 0                                                                       | 0          | 2           | 8          | 8                 | 0                                                              | 0          |
|          | Hair disorder                           | 0                                                                       | 0          | 1           | 7          | 7                 | 0                                                              | 0          |
|          | Hair growth abnormal                    | 0                                                                       | 0          | 3           | 7          | 7                 | 0                                                              | 0          |
|          | Hair growth rate abnormal               | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Hair texture abnormal                   | 0                                                                       | 1          | 9           | 12         | 13                | 0                                                              | 0          |
|          | Hand dermatitis                         | 1                                                                       | 3          | 6           | 10         | 13                | 0                                                              | 0          |
|          | Hangnail                                | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Heliotrope rash                         | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Henoch-Schonlein purpura                | 9                                                                       | 16         | 3           | 8          | 24                | 0                                                              | 0          |
|          | Herpes gestationis                      | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Hidradenitis                            | 3                                                                       | 4          | 3           | 5          | 9                 | 0                                                              | 0          |
|          | Hirsutism                               | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Hyperhidrosis                           | 1031                                                                    | 1323       | 1824        | 7149       | 8472              | 0                                                              | 0          |
|          | Hyperkeratosis                          | 0                                                                       | 1          | 3           | 9          | 10                | 0                                                              | 0          |
|          | Hypersensitivity vasculitis             | 8                                                                       | 10         | 0           | 0          | 10                | 0                                                              | 0          |
|          | Hypertrophic scar                       | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Hypohidrosis                            | 0                                                                       | 0          | 3           | 5          | 5                 | 0                                                              | 0          |
|          | Hypotrichosis                           | 1                                                                       | 1          | 2           | 2          | 3                 | 0                                                              | 0          |
|          | Ichthyosis acquired                     | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Idiopathic angioedema                   | 0                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Idiopathic urticaria                    | 3                                                                       | 3          | 5           | 6          | 9                 | 0                                                              | 0          |
|          | Ingrown hair                            | 2                                                                       | 2          | 0           | 2          | 4                 | 0                                                              | 0          |
|          | Interstitial granulomatous dermatitis   | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Intertrigo                              | 2                                                                       | 2          | 0           | 2          | 4                 | 0                                                              | 0          |
|          | Ischaemic skin ulcer                    | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |

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|----------|-------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                           | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                        | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Itching scar                              | 1                                                                       | 2          | 5           | 12         | 14                | 0                                                              | 0          |
|          | Keloid scar                               | 1                                                                       | 1          | 4           | 6          | 7                 | 0                                                              | 0          |
|          | Keratosis pilaris                         | 0                                                                       | 0          | 6           | 13         | 13                | 0                                                              | 0          |
|          | Leukoplakia                               | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Lichen planopilaris                       | 0                                                                       | 0          | 2           | 3          | 3                 | 0                                                              | 0          |
|          | Lichen planus                             | 7                                                                       | 9          | 12          | 24         | 33                | 0                                                              | 0          |
|          | Lichen sclerosis                          | 0                                                                       | 1          | 6           | 11         | 12                | 0                                                              | 0          |
|          | Lichenification                           | 0                                                                       | 0          | 2           | 2          | 2                 | 0                                                              | 0          |
|          | Lichenoid keratosis                       | 1                                                                       | 1          | 4           | 6          | 7                 | 0                                                              | 0          |
|          | Linear IgA disease                        | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Lipoatrophy                               | 0                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Lipodystrophy acquired                    | 2                                                                       | 2          | 0           | 1          | 3                 | 0                                                              | 0          |
|          | Lipohypertrophy                           | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|          | Livedo reticularis                        | 9                                                                       | 18         | 18          | 84         | 102               | 0                                                              | 0          |
|          | Lividity                                  | 2                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Lymphomatoid papulosis                    | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Macule                                    | 4                                                                       | 4          | 20          | 44         | 48                | 0                                                              | 0          |
|          | Madarosis                                 | 0                                                                       | 1          | 3           | 7          | 8                 | 0                                                              | 0          |
|          | Mechanical urticaria                      | 5                                                                       | 6          | 26          | 51         | 57                | 0                                                              | 0          |
|          | Melanoderma                               | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Milia                                     | 0                                                                       | 0          | 1           | 4          | 4                 | 0                                                              | 0          |
|          | Miliaria                                  | 18                                                                      | 23         | 34          | 94         | 117               | 0                                                              | 0          |
|          | Mucocutaneous disorder                    | 0                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Nail bed inflammation                     | 0                                                                       | 0          | 2           | 2          | 2                 | 0                                                              | 0          |
|          | Nail bed tenderness                       | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Nail discolouration                       | 0                                                                       | 1          | 6           | 18         | 19                | 0                                                              | 0          |
|          | Nail disorder                             | 5                                                                       | 7          | 2           | 6          | 13                | 0                                                              | 0          |
|          | Nail growth abnormal                      | 0                                                                       | 0          | 2           | 3          | 3                 | 0                                                              | 0          |
|          | Nail hypertrophy                          | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Nail psoriasis                            | 1                                                                       | 1          | 1           | 3          | 4                 | 0                                                              | 0          |
|          | Nail ridging                              | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Needle track marks                        | 0                                                                       | 0          | 5           | 6          | 6                 | 0                                                              | 0          |
|          | Neurodermatitis                           | 4                                                                       | 5          | 20          | 20         | 25                | 0                                                              | 0          |
|          | Neuropathic pruritus                      | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Neuropathic ulcer                         | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Neutrophilic dermatosis                   | 1                                                                       | 2          | 2           | 3          | 5                 | 0                                                              | 0          |
|          | Night sweats                              | 240                                                                     | 288        | 279         | 1110       | 1398              | 0                                                              | 0          |
|          | Nodular rash                              | 2                                                                       | 2          | 1           | 5          | 7                 | 0                                                              | 0          |
|          | Oculomucocutaneous syndrome               | 9                                                                       | 9          | 0           | 0          | 9                 | 0                                                              | 0          |
|          | Oedema blister                            | 0                                                                       | 0          | 0           | 3          | 3                 | 0                                                              | 0          |
|          | Onychalgia                                | 1                                                                       | 1          | 2           | 6          | 7                 | 0                                                              | 0          |
|          | Onychoclasia                              | 1                                                                       | 2          | 3           | 8          | 10                | 0                                                              | 0          |
|          | Onycholysis                               | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Onychomadesis                             | 2                                                                       | 2          | 0           | 3          | 5                 | 0                                                              | 0          |
|          | Pain of skin                              | 120                                                                     | 141        | 208         | 745        | 886               | 0                                                              | 0          |
|          | Palmar erythema                           | 2                                                                       | 3          | 4           | 16         | 19                | 0                                                              | 0          |
|          | Palmar-plantar erythrodysaesthesia syndro | 3                                                                       | 5          | 8           | 12         | 17                | 0                                                              | 0          |
|          | Palmoplantar pustulosis                   | 2                                                                       | 2          | 1           | 1          | 3                 | 0                                                              | 0          |
|          | Palpable purpura                          | 1                                                                       | 1          | 1           | 2          | 3                 | 0                                                              | 0          |

|          |                                               | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|-----------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                               | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                            | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Panniculitis                                  | 3                                                                       | 6          | 0           | 1          | 7                 | 0                                                              | 0          |
|          | Papule                                        | 8                                                                       | 10         | 60          | 146        | 156               | 0                                                              | 0          |
|          | Papulopustular rosacea                        | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Parakeratosis                                 | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|          | Parapsoriasis                                 | 1                                                                       | 1          | 2           | 2          | 3                 | 0                                                              | 0          |
|          | Peau d'orange                                 | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|          | Pemphigoid                                    | 34                                                                      | 48         | 3           | 4          | 52                | 0                                                              | 0          |
|          | Pemphigus                                     | 13                                                                      | 15         | 2           | 2          | 17                | 0                                                              | 0          |
|          | Perioral dermatitis                           | 0                                                                       | 1          | 4           | 10         | 11                | 0                                                              | 0          |
|          | Perivascular dermatitis                       | 3                                                                       | 3          | 1           | 1          | 4                 | 0                                                              | 0          |
|          | Pernio-like erythema                          | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Petechiae                                     | 75                                                                      | 156        | 155         | 331        | 487               | 0                                                              | 0          |
|          | Photodermatosis                               | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Photosensitivity reaction                     | 20                                                                      | 29         | 53          | 119        | 148               | 0                                                              | 0          |
|          | Pigmentation disorder                         | 4                                                                       | 6          | 19          | 41         | 47                | 0                                                              | 0          |
|          | Piloerection                                  | 12                                                                      | 13         | 16          | 51         | 64                | 0                                                              | 0          |
|          | Pityriasis                                    | 1                                                                       | 2          | 2           | 5          | 7                 | 0                                                              | 0          |
|          | Pityriasis lichenoides et varioliformis acuta | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Pityriasis rosea                              | 7                                                                       | 9          | 56          | 84         | 93                | 0                                                              | 0          |
|          | Pityriasis rubra pilaris                      | 2                                                                       | 2          | 1           | 3          | 5                 | 0                                                              | 0          |
|          | Plantar erythema                              | 1                                                                       | 1          | 2           | 2          | 3                 | 0                                                              | 0          |
|          | Polymorphic light eruption                    | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Post inflammatory pigmentation change         | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Prurigo                                       | 1                                                                       | 1          | 10          | 19         | 20                | 0                                                              | 0          |
|          | Pruritus                                      | 956                                                                     | 1347       | 4849        | 19495      | 20842             | 0                                                              | 0          |
|          | Pruritus allergic                             | 0                                                                       | 2          | 4           | 8          | 10                | 0                                                              | 0          |
|          | Psoriasis                                     | 31                                                                      | 40         | 61          | 153        | 193               | 0                                                              | 0          |
|          | Purpura                                       | 31                                                                      | 52         | 68          | 123        | 175               | 0                                                              | 0          |
|          | Purpura fulminans                             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Pustular psoriasis                            | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Pyoderma gangrenosum                          | 2                                                                       | 3          | 1           | 1          | 4                 | 0                                                              | 0          |
|          | Rash                                          | 1310                                                                    | 1867       | 5819        | 19024      | 20891             | 0                                                              | 0          |
|          | Rash erythematous                             | 288                                                                     | 411        | 834         | 5577       | 5988              | 0                                                              | 0          |
|          | Rash follicular                               | 0                                                                       | 0          | 2           | 3          | 3                 | 0                                                              | 0          |
|          | Rash macular                                  | 88                                                                      | 128        | 361         | 2122       | 2250              | 0                                                              | 0          |
|          | Rash maculo-papular                           | 19                                                                      | 34         | 77          | 193        | 227               | 0                                                              | 0          |
|          | Rash morbilliform                             | 2                                                                       | 4          | 17          | 66         | 70                | 0                                                              | 0          |
|          | Rash papular                                  | 59                                                                      | 89         | 176         | 1495       | 1584              | 0                                                              | 0          |
|          | Rash pruritic                                 | 182                                                                     | 272        | 861         | 4439       | 4711              | 0                                                              | 0          |
|          | Rash rubelliform                              | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Rash scarlatiniform                           | 1                                                                       | 1          | 2           | 5          | 6                 | 0                                                              | 0          |
|          | Rash vesicular                                | 20                                                                      | 27         | 52          | 211        | 238               | 0                                                              | 0          |
|          | Rebound psoriasis                             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Red man syndrome                              | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Rosacea                                       | 3                                                                       | 4          | 17          | 44         | 48                | 0                                                              | 0          |
|          | SJS-TEN overlap                               | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Scab                                          | 10                                                                      | 14         | 21          | 92         | 106               | 0                                                              | 0          |
|          | Scar pain                                     | 4                                                                       | 4          | 14          | 21         | 25                | 0                                                              | 0          |
|          | Seborrhoea                                    | 0                                                                       | 0          | 2           | 6          | 6                 | 0                                                              | 0          |



|          |                                  | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|----------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                  | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                               | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Seborrheic dermatitis            | 0                                                                       | 0          | 3           | 5          | 5                 | 0                                                              | 0          |
|          | Segmented hyalinising vasculitis | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Sensitive skin                   | 92                                                                      | 104        | 129         | 487        | 591               | 0                                                              | 0          |
|          | Skin atrophy                     | 2                                                                       | 3          | 4           | 11         | 14                | 0                                                              | 0          |
|          | Skin burning sensation           | 68                                                                      | 88         | 175         | 647        | 735               | 0                                                              | 0          |
|          | Skin depigmentation              | 3                                                                       | 3          | 3           | 8          | 11                | 0                                                              | 0          |
|          | Skin discharge                   | 1                                                                       | 1          | 3           | 4          | 5                 | 0                                                              | 0          |
|          | Skin discolouration              | 85                                                                      | 133        | 248         | 901        | 1034              | 0                                                              | 0          |
|          | Skin discomfort                  | 4                                                                       | 5          | 26          | 52         | 57                | 0                                                              | 0          |
|          | Skin disorder                    | 89                                                                      | 109        | 94          | 165        | 274               | 0                                                              | 0          |
|          | Skin dystrophy                   | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Skin erosion                     | 3                                                                       | 3          | 7           | 22         | 25                | 0                                                              | 0          |
|          | Skin exfoliation                 | 32                                                                      | 50         | 87          | 350        | 400               | 0                                                              | 0          |
|          | Skin fissures                    | 1                                                                       | 1          | 8           | 12         | 13                | 0                                                              | 0          |
|          | Skin fragility                   | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Skin haemorrhage                 | 5                                                                       | 10         | 29          | 61         | 71                | 0                                                              | 0          |
|          | Skin hyperpigmentation           | 1                                                                       | 1          | 7           | 24         | 25                | 0                                                              | 0          |
|          | Skin hypertrophy                 | 1                                                                       | 2          | 3           | 15         | 17                | 0                                                              | 0          |
|          | Skin hypopigmentation            | 1                                                                       | 1          | 2           | 3          | 4                 | 0                                                              | 0          |
|          | Skin indentation                 | 2                                                                       | 2          | 3           | 11         | 13                | 0                                                              | 0          |
|          | Skin induration                  | 2                                                                       | 2          | 13          | 128        | 130               | 0                                                              | 0          |
|          | Skin irritation                  | 24                                                                      | 28         | 58          | 235        | 263               | 0                                                              | 0          |
|          | Skin laxity                      | 0                                                                       | 0          | 1           | 3          | 3                 | 0                                                              | 0          |
|          | Skin lesion                      | 21                                                                      | 35         | 60          | 262        | 297               | 0                                                              | 0          |
|          | Skin lesion inflammation         | 0                                                                       | 0          | 0           | 4          | 4                 | 0                                                              | 0          |
|          | Skin maceration                  | 0                                                                       | 1          | 0           | 2          | 3                 | 0                                                              | 0          |
|          | Skin mass                        | 14                                                                      | 15         | 78          | 233        | 248               | 0                                                              | 0          |
|          | Skin necrosis                    | 5                                                                       | 12         | 1           | 1          | 13                | 0                                                              | 0          |
|          | Skin odour abnormal              | 4                                                                       | 4          | 12          | 31         | 35                | 0                                                              | 0          |
|          | Skin oedema                      | 1                                                                       | 2          | 5           | 11         | 13                | 0                                                              | 0          |
|          | Skin plaque                      | 4                                                                       | 6          | 19          | 36         | 42                | 0                                                              | 0          |
|          | Skin reaction                    | 71                                                                      | 98         | 777         | 1525       | 1623              | 0                                                              | 0          |
|          | Skin sensitisation               | 10                                                                      | 11         | 9           | 60         | 71                | 0                                                              | 0          |
|          | Skin striae                      | 1                                                                       | 1          | 1           | 7          | 8                 | 0                                                              | 0          |
|          | Skin swelling                    | 15                                                                      | 18         | 58          | 342        | 360               | 0                                                              | 0          |
|          | Skin texture abnormal            | 1                                                                       | 2          | 6           | 28         | 30                | 0                                                              | 0          |
|          | Skin tightness                   | 8                                                                       | 14         | 24          | 245        | 259               | 0                                                              | 0          |
|          | Skin ulcer                       | 24                                                                      | 28         | 11          | 37         | 65                | 0                                                              | 0          |
|          | Skin ulcer haemorrhage           | 1                                                                       | 1          | 1           | 2          | 3                 | 0                                                              | 0          |
|          | Skin warm                        | 106                                                                     | 178        | 227         | 4354       | 4532              | 0                                                              | 0          |
|          | Skin weeping                     | 6                                                                       | 10         | 4           | 25         | 35                | 0                                                              | 0          |
|          | Skin wrinkling                   | 3                                                                       | 3          | 7           | 25         | 28                | 0                                                              | 0          |
|          | Solar dermatitis                 | 0                                                                       | 0          | 2           | 3          | 3                 | 0                                                              | 0          |
|          | Solar lentigo                    | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Solar urticaria                  | 1                                                                       | 1          | 3           | 3          | 4                 | 0                                                              | 0          |
|          | Spider naevus                    | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Splinter haemorrhages            | 0                                                                       | 0          | 2           | 3          | 3                 | 0                                                              | 0          |
|          | Stasis dermatitis                | 1                                                                       | 2          | 1           | 1          | 3                 | 0                                                              | 0          |
|          | Stevens-Johnson syndrome         | 21                                                                      | 38         | 0           | 0          | 38                | 0                                                              | 0          |

|                      |                                             | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------------------|---------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|                      |                                             | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM             | PT                                          | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|                      | Sticky skin                                 | 0                                                                       | 0          | 0           | 10         | 10                | 0                                                              | 0          |
|                      | Subacute cutaneous lupus erythematosus      | 5                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|                      | Subcutaneous drug absorption impaired       | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|                      | Subcutaneous emphysema                      | 3                                                                       | 3          | 1           | 2          | 5                 | 0                                                              | 0          |
|                      | Sweat discolouration                        | 0                                                                       | 0          | 1           | 3          | 3                 | 0                                                              | 0          |
|                      | Symmetrical drug-related intertriginous and | 2                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|                      | Systemic lupus erythematosus rash           | 0                                                                       | 1          | 0           | 3          | 4                 | 0                                                              | 0          |
|                      | Target skin lesion                          | 2                                                                       | 5          | 1           | 1          | 6                 | 0                                                              | 0          |
|                      | Telangiectasia                              | 0                                                                       | 0          | 4           | 7          | 7                 | 0                                                              | 0          |
|                      | Toxic epidermal necrolysis                  | 2                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|                      | Toxic skin eruption                         | 8                                                                       | 11         | 0           | 0          | 11                | 0                                                              | 0          |
|                      | Transient acantholytic dermatosis           | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|                      | Trichodynia                                 | 0                                                                       | 0          | 3           | 3          | 3                 | 0                                                              | 0          |
|                      | Trichorrhexis                               | 0                                                                       | 0          | 2           | 5          | 5                 | 0                                                              | 0          |
|                      | Urticaria                                   | 524                                                                     | 811        | 2415        | 9007       | 9818              | 0                                                              | 0          |
|                      | Urticaria aquagenic                         | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                      | Urticaria cholinergic                       | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|                      | Urticaria chronic                           | 10                                                                      | 10         | 12          | 14         | 24                | 0                                                              | 0          |
|                      | Urticaria contact                           | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|                      | Urticaria papular                           | 0                                                                       | 2          | 5           | 14         | 16                | 0                                                              | 0          |
|                      | Urticaria pressure                          | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|                      | Urticaria thermal                           | 0                                                                       | 0          | 3           | 4          | 4                 | 0                                                              | 0          |
|                      | Urticaria vesiculosa                        | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|                      | Urticarial dermatitis                       | 0                                                                       | 0          | 2           | 3          | 3                 | 0                                                              | 0          |
|                      | Urticarial vasculitis                       | 10                                                                      | 11         | 0           | 0          | 11                | 0                                                              | 0          |
|                      | Vascular purpura                            | 3                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|                      | Vasculitic rash                             | 2                                                                       | 4          | 2           | 6          | 10                | 0                                                              | 0          |
|                      | Venous ulcer pain                           | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                      | Vitiligo                                    | 9                                                                       | 9          | 14          | 23         | 32                | 0                                                              | 0          |
|                      | Yellow skin                                 | 5                                                                       | 9          | 9           | 33         | 42                | 0                                                              | 0          |
| Social circumstances | *** SOC TOTAL ***                           | 856                                                                     | 1291       | 1134        | 3932       | 5223              | 0                                                              | 0          |
|                      | Abstains from alcohol                       | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                      | Abstains from recreational drugs            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                      | Alcohol use                                 | 3                                                                       | 3          | 0           | 3          | 6                 | 0                                                              | 0          |
|                      | Anal sex                                    | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                      | Bedridden                                   | 38                                                                      | 60         | 221         | 492        | 552               | 0                                                              | 0          |
|                      | Blood donor                                 | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|                      | Blood product transfusion dependent         | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                      | Bottle feeding                              | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|                      | Breast feeding                              | 2                                                                       | 3          | 3           | 26         | 29                | 0                                                              | 0          |
|                      | Cardiac assistance device user              | 9                                                                       | 12         | 1           | 2          | 14                | 0                                                              | 0          |
|                      | Caregiver                                   | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|                      | Contraindication to medical treatment       | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                      | Contraindication to vaccination             | 0                                                                       | 3          | 0           | 4          | 7                 | 0                                                              | 0          |
|                      | Convalescent                                | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                      | Corrective lens user                        | 1                                                                       | 1          | 1           | 2          | 3                 | 0                                                              | 0          |
|                      | Death of pet                                | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|                      | Dependence on oxygen therapy                | 5                                                                       | 8          | 0           | 0          | 8                 | 0                                                              | 0          |
|                      | Device dependence                           | 0                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |

|          |                                                   | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|---------------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                                   | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                                | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Disability                                        | 24                                                                      | 44         | 1           | 3          | 47                | 0                                                              | 0          |
|          | Economic problem                                  | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Ex-tobacco user                                   | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Exercise lack of                                  | 0                                                                       | 1          | 1           | 5          | 6                 | 0                                                              | 0          |
|          | Familial risk factor                              | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|          | Family stress                                     | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|          | Fasting                                           | 0                                                                       | 1          | 1           | 8          | 9                 | 0                                                              | 0          |
|          | Feeding tube user                                 | 3                                                                       | 8          | 1           | 2          | 10                | 0                                                              | 0          |
|          | Foot prosthesis user                              | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Foreign travel                                    | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Hearing aid user                                  | 3                                                                       | 3          | 1           | 1          | 4                 | 0                                                              | 0          |
|          | Hearing disability                                | 2                                                                       | 3          | 4           | 7          | 10                | 0                                                              | 0          |
|          | Housebound                                        | 2                                                                       | 4          | 2           | 3          | 7                 | 0                                                              | 0          |
|          | Illiteracy                                        | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Immobile                                          | 14                                                                      | 47         | 4           | 9          | 56                | 0                                                              | 0          |
|          | Immobilisation prolonged                          | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Impaired ability to use machinery                 | 2                                                                       | 2          | 1           | 2          | 4                 | 0                                                              | 0          |
|          | Impaired driving ability                          | 73                                                                      | 115        | 61          | 220        | 335               | 0                                                              | 0          |
|          | Impaired quality of life                          | 16                                                                      | 19         | 20          | 36         | 55                | 0                                                              | 0          |
|          | Impaired work ability                             | 268                                                                     | 389        | 377         | 1686       | 2075              | 0                                                              | 0          |
|          | Imprisonment                                      | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Inability to afford medication                    | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Inadequate diet                                   | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Insurance issue                                   | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Job dissatisfaction                               | 0                                                                       | 0          | 3           | 7          | 7                 | 0                                                              | 0          |
|          | Living alone                                      | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Loss of employment                                | 2                                                                       | 2          | 3           | 4          | 6                 | 0                                                              | 0          |
|          | Loss of personal independence in daily activities | 221                                                                     | 336        | 349         | 1173       | 1509              | 0                                                              | 0          |
|          | Menarche                                          | 2                                                                       | 2          | 0           | 1          | 3                 | 0                                                              | 0          |
|          | Menopause                                         | 4                                                                       | 6          | 6           | 18         | 24                | 0                                                              | 0          |
|          | Mental disability                                 | 0                                                                       | 0          | 0           | 3          | 3                 | 0                                                              | 0          |
|          | Multigravida                                      | 0                                                                       | 1          | 0           | 2          | 3                 | 0                                                              | 0          |
|          | Non-tobacco user                                  | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Organ donor                                       | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Orthosis user                                     | 6                                                                       | 6          | 0           | 1          | 7                 | 0                                                              | 0          |
|          | Overwork                                          | 0                                                                       | 0          | 4           | 4          | 4                 | 0                                                              | 0          |
|          | Paralytic disability                              | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Patient uncooperative                             | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Physical assault                                  | 1                                                                       | 1          | 1           | 2          | 3                 | 0                                                              | 0          |
|          | Physical disability                               | 5                                                                       | 5          | 2           | 6          | 11                | 0                                                              | 0          |
|          | Planning to become pregnant                       | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Postmenopause                                     | 0                                                                       | 1          | 0           | 2          | 3                 | 0                                                              | 0          |
|          | Refusal of examination                            | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Refusal of treatment by patient                   | 3                                                                       | 7          | 1           | 10         | 17                | 0                                                              | 0          |
|          | Refusal of treatment by relative                  | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Refusal of vaccination                            | 1                                                                       | 1          | 0           | 6          | 7                 | 0                                                              | 0          |
|          | Retirement                                        | 1                                                                       | 1          | 1           | 2          | 3                 | 0                                                              | 0          |
|          | Sick leave                                        | 2                                                                       | 2          | 3           | 3          | 5                 | 0                                                              | 0          |
|          | Sick relative                                     | 3                                                                       | 3          | 0           | 2          | 5                 | 0                                                              | 0          |

|                                 |                                 | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|---------------------------------|---------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|                                 |                                 | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM                        | PT                              | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|                                 | Sight disability                | 3                                                                       | 4          | 3           | 5          | 9                 | 0                                                              | 0          |
|                                 | Sitting disability              | 11                                                                      | 12         | 10          | 27         | 39                | 0                                                              | 0          |
|                                 | Social problem                  | 1                                                                       | 1          | 2           | 2          | 3                 | 0                                                              | 0          |
|                                 | Spousal abuse                   | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                 | Stress at work                  | 1                                                                       | 1          | 2           | 4          | 5                 | 0                                                              | 0          |
|                                 | Substance use                   | 1                                                                       | 1          | 0           | 5          | 6                 | 0                                                              | 0          |
|                                 | Tanning                         | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|                                 | Tattoo                          | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|                                 | Threat of redundancy            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                 | Tobacco user                    | 4                                                                       | 4          | 0           | 1          | 5                 | 0                                                              | 0          |
|                                 | Unemployment                    | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|                                 | Unhealthy diet                  | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|                                 | Vegan                           | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|                                 | Victim of abuse                 | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                 | Walking aid user                | 60                                                                      | 91         | 32          | 78         | 169               | 0                                                              | 0          |
|                                 | Walking disability              | 6                                                                       | 11         | 3           | 10         | 21                | 0                                                              | 0          |
|                                 | Water pollution                 | 3                                                                       | 4          | 1           | 5          | 9                 | 0                                                              | 0          |
|                                 | Wheelchair user                 | 27                                                                      | 34         | 5           | 16         | 50                | 0                                                              | 0          |
| Surgical and medical procedures | *** SOC TOTAL ***               | 1595                                                                    | 2142       | 1216        | 2326       | 4468              | 0                                                              | 0          |
|                                 | Abdominal cavity drainage       | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                                 | Abortion induced                | 4                                                                       | 8          | 0           | 4          | 12                | 0                                                              | 0          |
|                                 | Abscess drainage                | 1                                                                       | 3          | 0           | 7          | 10                | 0                                                              | 0          |
|                                 | Acrochordon excision            | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|                                 | Acupuncture                     | 2                                                                       | 2          | 0           | 1          | 3                 | 0                                                              | 0          |
|                                 | Adhesiolysis                    | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                 | Airway patency device insertion | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                 | Amputation                      | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                                 | Anaesthesia procedure           | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|                                 | Analgesic therapy               | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|                                 | Anaphylaxis prophylaxis         | 0                                                                       | 0          | 0           | 8          | 8                 | 0                                                              | 0          |
|                                 | Anaphylaxis treatment           | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|                                 | Aneurysm repair                 | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                                 | Aneurysmectomy                  | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|                                 | Angioplasty                     | 1                                                                       | 6          | 0           | 1          | 7                 | 0                                                              | 0          |
|                                 | Ankle operation                 | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                                 | Antiallergic therapy            | 0                                                                       | 0          | 2           | 2          | 2                 | 0                                                              | 0          |
|                                 | Antibiotic therapy              | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|                                 | Anticoagulant therapy           | 190                                                                     | 216        | 11          | 12         | 228               | 0                                                              | 0          |
|                                 | Antidepressant therapy          | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|                                 | Antiplatelet therapy            | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                                 | Aortic aneurysm repair          | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                 | Aortic valve repair             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                 | Aortic valve replacement        | 4                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|                                 | Apheresis                       | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                 | Appendicectomy                  | 19                                                                      | 30         | 2           | 6          | 36                | 0                                                              | 0          |
|                                 | Arterial angioplasty            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                 | Arterial catheterisation        | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                 | Arterial repair                 | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                                 | Arterial stent insertion        | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |

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|----------|---------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                       | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                    | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Arteriovenous fistula operation       | 1                                                                       | 2          | 0           | 1          | 3                 | 0                                                              | 0          |
|          | Arthroscopic surgery                  | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Artificial insemination               | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Artificial skin graft                 | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Asthma prophylaxis                    | 1                                                                       | 1          | 0           | 3          | 4                 | 0                                                              | 0          |
|          | Atrial appendage closure              | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Atrial appendage resection            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Axillary lymphadenectomy              | 0                                                                       | 0          | 1           | 6          | 6                 | 0                                                              | 0          |
|          | Bed rest                              | 11                                                                      | 12         | 16          | 77         | 89                | 0                                                              | 0          |
|          | Behavioural therapy                   | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Bile duct stent insertion             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Bladder catheter permanent            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Bladder catheter removal              | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Bladder catheterisation               | 14                                                                      | 16         | 1           | 2          | 18                | 0                                                              | 0          |
|          | Bladder operation                     | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Blood donation                        | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Botulinum toxin injection             | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Brain operation                       | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Breast conserving surgery             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Breast operation                      | 0                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | COVID-19 immunisation                 | 112                                                                     | 118        | 292         | 317        | 435               | 0                                                              | 0          |
|          | Caesarean section                     | 10                                                                      | 13         | 1           | 3          | 16                | 0                                                              | 0          |
|          | Canalith repositioning procedure      | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Cancer surgery                        | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|          | Cardiac ablation                      | 15                                                                      | 17         | 2           | 2          | 19                | 0                                                              | 0          |
|          | Cardiac operation                     | 4                                                                       | 8          | 1           | 4          | 12                | 0                                                              | 0          |
|          | Cardiac pacemaker insertion           | 23                                                                      | 31         | 2           | 3          | 34                | 0                                                              | 0          |
|          | Cardiac pacemaker replacement         | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Cardiac resynchronisation therapy     | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Cardiopulmonary bypass                | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Cardioversion                         | 37                                                                      | 42         | 11          | 16         | 58                | 0                                                              | 0          |
|          | Carotid artery bypass                 | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Carotid artery stent insertion        | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Carotid endarterectomy                | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Carpal tunnel decompression           | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Cast application                      | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Cataract operation                    | 2                                                                       | 2          | 1           | 1          | 3                 | 0                                                              | 0          |
|          | Catheter management                   | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|          | Catheter placement                    | 6                                                                       | 7          | 0           | 0          | 7                 | 0                                                              | 0          |
|          | Catheter removal                      | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Cautery to nose                       | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|          | Central nervous system stimulation    | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Central venous catheterisation        | 9                                                                       | 9          | 0           | 0          | 9                 | 0                                                              | 0          |
|          | Cerebral artery stent insertion       | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Cerebral endovascular aneurysm repair | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Cerebrospinal fluid drainage          | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Cerumen removal                       | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Chemotherapy                          | 7                                                                       | 8          | 1           | 2          | 10                | 0                                                              | 0          |
|          | Chest tube insertion                  | 8                                                                       | 9          | 0           | 0          | 9                 | 0                                                              | 0          |

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|          |                                     | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                  | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Chest tube removal                  | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Chiropractic                        | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Cholecystectomy                     | 6                                                                       | 16         | 1           | 3          | 19                | 0                                                              | 0          |
|          | Cholelithotomy                      | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Cochlea implant                     | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Colectomy                           | 2                                                                       | 3          | 0           | 1          | 4                 | 0                                                              | 0          |
|          | Colectomy total                     | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Colon operation                     | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Colonic lavage                      | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Colostomy                           | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Compression garment application     | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Contraception                       | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Cooling therapy                     | 0                                                                       | 0          | 0           | 4          | 4                 | 0                                                              | 0          |
|          | Coronary angioplasty                | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Coronary arterial stent insertion   | 20                                                                      | 27         | 0           | 1          | 28                | 0                                                              | 0          |
|          | Coronary artery bypass              | 8                                                                       | 9          | 0           | 1          | 10                | 0                                                              | 0          |
|          | Cows milk free diet                 | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Cranioplasty                        | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Craniotomy                          | 2                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Cryotherapy                         | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Cyst drainage                       | 1                                                                       | 2          | 0           | 2          | 4                 | 0                                                              | 0          |
|          | Debridement                         | 4                                                                       | 4          | 0           | 1          | 5                 | 0                                                              | 0          |
|          | Decompressive craniectomy           | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Dental care                         | 0                                                                       | 0          | 1           | 3          | 3                 | 0                                                              | 0          |
|          | Dental impression procedure         | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Dental operation                    | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|          | Depilation                          | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Dermal filler injection             | 2                                                                       | 3          | 0           | 6          | 9                 | 0                                                              | 0          |
|          | Detoxification                      | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Diabetes mellitus management        | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Diabetic diet                       | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Dialysis                            | 14                                                                      | 20         | 0           | 0          | 20                | 0                                                              | 0          |
|          | Dialysis device insertion           | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Diuretic therapy                    | 4                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Drain placement                     | 3                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Drainage                            | 3                                                                       | 3          | 1           | 19         | 22                | 0                                                              | 0          |
|          | Drug withdrawal maintenance therapy | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Ear irrigation                      | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Ear tube insertion                  | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Ectopic pregnancy termination       | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Elective procedure                  | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Electrocauterisation                | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Electroconvulsive therapy           | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Electrolyte substitution therapy    | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Emergency care                      | 0                                                                       | 0          | 0           | 7          | 7                 | 0                                                              | 0          |
|          | Endarterectomy                      | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Endobronchial valve implantation    | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Endodontic procedure                | 0                                                                       | 0          | 1           | 5          | 5                 | 0                                                              | 0          |
|          | Endometrial ablation                | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |

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|          |                                       | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                    | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Endotracheal intubation               | 102                                                                     | 129        | 1           | 3          | 132               | 0                                                              | 0          |
|          | Enteral nutrition                     | 2                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Epidural injection                    | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Euthanasia                            | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Explorative laparotomy                | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Exploratory operation                 | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Extubation                            | 7                                                                       | 8          | 0           | 0          | 8                 | 0                                                              | 0          |
|          | Eye drop instillation                 | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Eye exercises                         | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Eye irrigation                        | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Eye laser surgery                     | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Eye muscle recession                  | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Eye operation                         | 2                                                                       | 2          | 1           | 2          | 4                 | 0                                                              | 0          |
|          | Eyeglasses therapy                    | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Eyelid cyst removal                   | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Faecal disimpaction                   | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Fallopian tube operation              | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Fascial operation                     | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Fasciotomy                            | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Finger amputation                     | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Fluid intake restriction              | 6                                                                       | 7          | 0           | 0          | 7                 | 0                                                              | 0          |
|          | Fluid replacement                     | 0                                                                       | 0          | 0           | 3          | 3                 | 0                                                              | 0          |
|          | Foot amputation                       | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Foot operation                        | 0                                                                       | 1          | 1           | 2          | 3                 | 0                                                              | 0          |
|          | Fraction of inspired oxygen           | 4                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Gallbladder operation                 | 0                                                                       | 2          | 1           | 1          | 3                 | 0                                                              | 0          |
|          | Gastrointestinal decompression        | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Gastrointestinal disorder prophylaxis | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Gastrointestinal tube insertion       | 6                                                                       | 8          | 0           | 1          | 9                 | 0                                                              | 0          |
|          | Gastrointestinal tube removal         | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Gastrostomy                           | 4                                                                       | 6          | 0           | 0          | 6                 | 0                                                              | 0          |
|          | Gluten free diet                      | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Haematoma evacuation                  | 0                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Haemodialysis                         | 18                                                                      | 19         | 0           | 0          | 19                | 0                                                              | 0          |
|          | Haemofiltration                       | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Haemorrhoid operation                 | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Haemostasis                           | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Hearing aid therapy                   | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Heart valve operation                 | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Heat therapy                          | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Hepatectomy                           | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Hepatic embolisation                  | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Hepatitis B immunisation              | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Hernia hiatus repair                  | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Hernia repair                         | 1                                                                       | 1          | 0           | 2          | 3                 | 0                                                              | 0          |
|          | High intensity focused ultrasound     | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Hip arthroplasty                      | 3                                                                       | 4          | 1           | 6          | 10                | 0                                                              | 0          |
|          | Hip surgery                           | 2                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Hormonal contraception                | 0                                                                       | 0          | 2           | 2          | 2                 | 0                                                              | 0          |

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|          |                                       | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                    | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Hormone therapy                       | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Hospice care                          | 0                                                                       | 3          | 1           | 2          | 5                 | 0                                                              | 0          |
|          | Hospitalisation                       | 78                                                                      | 252        | 3           | 4          | 256               | 0                                                              | 0          |
|          | Hyperbaric oxygen therapy             | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Hysterectomy                          | 0                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Ileostomy                             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Immune enhancement therapy            | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Immunisation                          | 13                                                                      | 13         | 17          | 57         | 70                | 0                                                              | 0          |
|          | Immunochemotherapy                    | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Immunoglobulin therapy                | 20                                                                      | 26         | 0           | 0          | 26                | 0                                                              | 0          |
|          | Immunosuppressant drug therapy        | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Implantable cardiac monitor insertion | 5                                                                       | 6          | 0           | 0          | 6                 | 0                                                              | 0          |
|          | Implantable defibrillator insertion   | 2                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | In vitro fertilisation                | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Incentive spirometry                  | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Incisional drainage                   | 3                                                                       | 4          | 0           | 1          | 5                 | 0                                                              | 0          |
|          | Infection prophylaxis                 | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Influenza immunisation                | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|          | Infusion                              | 8                                                                       | 11         | 5           | 8          | 19                | 0                                                              | 0          |
|          | Inguinal hernia repair                | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Injection                             | 8                                                                       | 8          | 4           | 7          | 15                | 0                                                              | 0          |
|          | Inner ear operation                   | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Insulin therapy                       | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Intensive care                        | 152                                                                     | 176        | 2           | 3          | 179               | 0                                                              | 0          |
|          | Interchange of vaccine products       | 39                                                                      | 42         | 704         | 1327       | 1369              | 0                                                              | 0          |
|          | Internal fixation of fracture         | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Intestinal resection                  | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Intramedullary rod insertion          | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Intraosseous access placement         | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Intrauterine contraception            | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Joint arthroplasty                    | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Joint fluid drainage                  | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Joint injection                       | 4                                                                       | 4          | 2           | 4          | 8                 | 0                                                              | 0          |
|          | Joint stabilisation                   | 0                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Knee arthroplasty                     | 8                                                                       | 10         | 0           | 7          | 17                | 0                                                              | 0          |
|          | Knee operation                        | 2                                                                       | 2          | 1           | 6          | 8                 | 0                                                              | 0          |
|          | Labour induction                      | 3                                                                       | 3          | 1           | 1          | 4                 | 0                                                              | 0          |
|          | Labour stimulation                    | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Laparoscopic surgery                  | 3                                                                       | 4          | 1           | 1          | 5                 | 0                                                              | 0          |
|          | Laparotomy                            | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Large intestinal polypectomy          | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Leg amputation                        | 5                                                                       | 7          | 0           | 0          | 7                 | 0                                                              | 0          |
|          | Lesion excision                       | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Life support                          | 5                                                                       | 9          | 0           | 1          | 10                | 0                                                              | 0          |
|          | Limb immobilisation                   | 2                                                                       | 3          | 1           | 24         | 27                | 0                                                              | 0          |
|          | Limb operation                        | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Lip cosmetic procedure                | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Lipolysis procedure                   | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Lipoma excision                       | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |



|          |                                             | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|---------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                             | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                          | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Liver transplant                            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Lung assist device therapy                  | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Lung lobectomy                              | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Lung transplant                             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Lymphadenectomy                             | 5                                                                       | 5          | 0           | 1          | 6                 | 0                                                              | 0          |
|          | Magnetic therapy                            | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Manual lymphatic drainage                   | 1                                                                       | 1          | 0           | 2          | 3                 | 0                                                              | 0          |
|          | Mass excision                               | 0                                                                       | 0          | 1           | 12         | 12                | 0                                                              | 0          |
|          | Mastectomy                                  | 2                                                                       | 2          | 0           | 2          | 4                 | 0                                                              | 0          |
|          | Mechanical ventilation                      | 40                                                                      | 57         | 2           | 5          | 62                | 0                                                              | 0          |
|          | Medical device removal                      | 2                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Medical diet                                | 2                                                                       | 3          | 0           | 1          | 4                 | 0                                                              | 0          |
|          | Medical induction of coma                   | 3                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Medical procedure                           | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Menstrual cycle management                  | 1                                                                       | 1          | 34          | 37         | 38                | 0                                                              | 0          |
|          | Micrographic skin surgery                   | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Mineral supplementation                     | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Mitral valve repair                         | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Mitral valve replacement                    | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Monoclonal antibody immunoconjugate therapy | 1                                                                       | 1          | 2           | 2          | 3                 | 0                                                              | 0          |
|          | Nasal cavity packing                        | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Nasal operation                             | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Neck surgery                                | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Nephrostomy                                 | 0                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Nerve block                                 | 2                                                                       | 3          | 4           | 7          | 10                | 0                                                              | 0          |
|          | Neurosurgery                                | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Nitrate compound therapy                    | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Nothing by mouth order                      | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Office visit                                | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Omentectomy                                 | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Oophorectomy                                | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Open reduction of fracture                  | 3                                                                       | 3          | 0           | 1          | 4                 | 0                                                              | 0          |
|          | Oral contraception                          | 0                                                                       | 0          | 5           | 6          | 6                 | 0                                                              | 0          |
|          | Oral surgery                                | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Orchidectomy                                | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Ostomy bag placement                        | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Ovarian operation                           | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Ovulation induction                         | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Oxygen therapy                              | 1                                                                       | 1          | 1           | 3          | 4                 | 0                                                              | 0          |
|          | Pacemaker generated rhythm                  | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Packed red blood cell transfusion           | 5                                                                       | 6          | 0           | 0          | 6                 | 0                                                              | 0          |
|          | Pain management                             | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Pancreatectomy                              | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Parenteral nutrition                        | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Patient isolation                           | 3                                                                       | 3          | 1           | 4          | 7                 | 0                                                              | 0          |
|          | Patient restraint                           | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Pelvic floor muscle training                | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Pelvic operation                            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Percutaneous coronary intervention          | 2                                                                       | 6          | 0           | 0          | 6                 | 0                                                              | 0          |

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|----------|--------------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                            | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                         | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Pericardial drainage                       | 9                                                                       | 10         | 0           | 0          | 10                | 0                                                              | 0          |
|          | Pericardial excision                       | 4                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Peripheral nerve decompression             | 0                                                                       | 1          | 0           | 2          | 3                 | 0                                                              | 0          |
|          | Peripheral nerve neurostimulation          | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Peripheral nerve operation                 | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Physiotherapy                              | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Physiotherapy chest                        | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Plasmapheresis                             | 7                                                                       | 8          | 1           | 1          | 9                 | 0                                                              | 0          |
|          | Platelet transfusion                       | 3                                                                       | 5          | 1           | 1          | 6                 | 0                                                              | 0          |
|          | Pleural decortication                      | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Pneumococcal immunisation                  | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|          | Polypectomy                                | 1                                                                       | 1          | 0           | 2          | 3                 | 0                                                              | 0          |
|          | Positive airway pressure therapy           | 59                                                                      | 65         | 2           | 3          | 68                | 0                                                              | 0          |
|          | Post procedural drainage                   | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Posterior fossa decompression              | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Preoperative care                          | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Product substitution                       | 0                                                                       | 0          | 0           | 3          | 3                 | 0                                                              | 0          |
|          | Prone position                             | 6                                                                       | 6          | 0           | 1          | 7                 | 0                                                              | 0          |
|          | Prophylaxis of nausea and vomiting         | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Prostatectomy                              | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Prostatic operation                        | 1                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Pulmonary endarterectomy                   | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Pulmonary resection                        | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Pulmonary valve replacement                | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Quarantine                                 | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|          | Radical hysterectomy                       | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Radiotherapy                               | 2                                                                       | 2          | 1           | 1          | 3                 | 0                                                              | 0          |
|          | Radiotherapy to lymph nodes                | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Rehabilitation therapy                     | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Removal of foreign body from oesophagus    | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Removal of inert matter from skin or subcu | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Renal stone removal                        | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|          | Renal transplant                           | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Resuscitation                              | 41                                                                      | 60         | 1           | 4          | 64                | 0                                                              | 0          |
|          | Salpingectomy                              | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Sedative therapy                           | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Seizure prophylaxis                        | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Self-medication                            | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Seroma drainage                            | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Shoulder arthroplasty                      | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Shoulder operation                         | 1                                                                       | 1          | 2           | 3          | 4                 | 0                                                              | 0          |
|          | Sinus operation                            | 4                                                                       | 4          | 3           | 25         | 29                | 0                                                              | 0          |
|          | Skin implant                               | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Small intestinal resection                 | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Smoking cessation therapy                  | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Specialist consultation                    | 2                                                                       | 2          | 3           | 9          | 11                | 0                                                              | 0          |
|          | Spinal cord operation                      | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Spinal decompression                       | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Spinal fusion surgery                      | 3                                                                       | 3          | 0           | 1          | 4                 | 0                                                              | 0          |

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|----------|--------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                      | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                   | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Spinal laminectomy                   | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Spinal manipulation                  | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Spinal nerve stimulator implantation | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Spinal operation                     | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Splenectomy                          | 3                                                                       | 7          | 0           | 0          | 7                 | 0                                                              | 0          |
|          | Splenic artery embolisation          | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Splint application                   | 2                                                                       | 2          | 0           | 1          | 3                 | 0                                                              | 0          |
|          | Stem cell transplant                 | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|          | Stent placement                      | 15                                                                      | 25         | 1           | 6          | 31                | 0                                                              | 0          |
|          | Stent removal                        | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Sternotomy                           | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Steroid therapy                      | 0                                                                       | 1          | 1           | 2          | 3                 | 0                                                              | 0          |
|          | Subdural haematoma evacuation        | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Surgery                              | 32                                                                      | 42         | 5           | 22         | 64                | 0                                                              | 0          |
|          | Suture insertion                     | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Tendon sheath incision               | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Tenotomy                             | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Tetanus immunisation                 | 0                                                                       | 0          | 0           | 3          | 3                 | 0                                                              | 0          |
|          | Therapeutic embolisation             | 2                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Therapeutic gargle                   | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Therapeutic hypothermia              | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Therapeutic procedure                | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Therapy cessation                    | 2                                                                       | 2          | 0           | 3          | 5                 | 0                                                              | 0          |
|          | Therapy change                       | 0                                                                       | 0          | 1           | 3          | 3                 | 0                                                              | 0          |
|          | Therapy interrupted                  | 1                                                                       | 1          | 2           | 5          | 6                 | 0                                                              | 0          |
|          | Thoracic cavity drainage             | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Thoracic operation                   | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Thoracotomy                          | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Thrombectomy                         | 24                                                                      | 33         | 1           | 2          | 35                | 0                                                              | 0          |
|          | Thromboembolectomy                   | 2                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Thrombolysis                         | 4                                                                       | 9          | 0           | 0          | 9                 | 0                                                              | 0          |
|          | Thymectomy                           | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Thyroidectomy                        | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Toe amputation                       | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Tonsillectomy                        | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Tooth extraction                     | 4                                                                       | 4          | 5           | 12         | 16                | 0                                                              | 0          |
|          | Tooth restoration                    | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Tracheostomy                         | 4                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Tracheostomy tube removal            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Transfusion                          | 16                                                                      | 26         | 3           | 9          | 35                | 0                                                              | 0          |
|          | Transplant                           | 0                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Trendelenburg position               | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Tumour excision                      | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Ureteral stent insertion             | 4                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Urethral bulking agent injection     | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Uterine dilation and curettage       | 6                                                                       | 10         | 0           | 3          | 13                | 0                                                              | 0          |
|          | Uterine dilation and evacuation      | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Vagal nerve stimulator implantation  | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Varicose vein operation              | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |

|                    |                                     | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|--------------------|-------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|                    |                                     | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM           | PT                                  | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|                    | Vascular graft                      | 1                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|                    | Vascular operation                  | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                    | Vasodilation procedure              | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                    | Vena cava filter insertion          | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|                    | Vena cava filter removal            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                    | Ventricular assist device insertion | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                    | Ventricular cisternostomy           | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                    | Ventricular drainage                | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                    | Vessel harvesting                   | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                    | Vitrectomy                          | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                    | Vocal cord polypectomy              | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                    | Volvulus repair                     | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                    | Wean from ventilator                | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                    | Withdrawal of life support          | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                    | Wound closure                       | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|                    | Wound drainage                      | 0                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|                    | Wound treatment                     | 3                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|                    | X-ray therapy to lung               | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
| Vascular disorders | *** SOC TOTAL ***                   | 4397                                                                    | 7689       | 3684        | 11913      | 19602             | 0                                                              | 0          |
|                    | Accelerated hypertension            | 2                                                                       | 8          | 1           | 2          | 10                | 0                                                              | 0          |
|                    | Achenbach syndrome                  | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|                    | Air embolism                        | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                    | Aneurysm                            | 8                                                                       | 21         | 2           | 4          | 25                | 0                                                              | 0          |
|                    | Aneurysm ruptured                   | 4                                                                       | 6          | 0           | 0          | 6                 | 0                                                              | 0          |
|                    | Angiodysplasia                      | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                    | Angiopathy                          | 7                                                                       | 9          | 6           | 12         | 21                | 0                                                              | 0          |
|                    | Aortic aneurysm                     | 14                                                                      | 20         | 1           | 5          | 25                | 0                                                              | 0          |
|                    | Aortic aneurysm rupture             | 3                                                                       | 8          | 0           | 0          | 8                 | 0                                                              | 0          |
|                    | Aortic arteriosclerosis             | 21                                                                      | 27         | 0           | 2          | 29                | 0                                                              | 0          |
|                    | Aortic dilatation                   | 5                                                                       | 9          | 0           | 0          | 9                 | 0                                                              | 0          |
|                    | Aortic disorder                     | 4                                                                       | 4          | 1           | 1          | 5                 | 0                                                              | 0          |
|                    | Aortic dissection                   | 20                                                                      | 31         | 0           | 0          | 31                | 0                                                              | 0          |
|                    | Aortic dissection rupture           | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                    | Aortic embolus                      | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                    | Aortic occlusion                    | 4                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|                    | Aortic perforation                  | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                    | Aortic rupture                      | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                    | Aortic stenosis                     | 5                                                                       | 12         | 0           | 1          | 13                | 0                                                              | 0          |
|                    | Aortic thrombosis                   | 8                                                                       | 14         | 0           | 0          | 14                | 0                                                              | 0          |
|                    | Aortitis                            | 3                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|                    | Arterial disorder                   | 0                                                                       | 0          | 2           | 4          | 4                 | 0                                                              | 0          |
|                    | Arterial haemorrhage                | 0                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|                    | Arterial occlusive disease          | 9                                                                       | 15         | 2           | 4          | 19                | 0                                                              | 0          |
|                    | Arterial rupture                    | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|                    | Arterial spasm                      | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|                    | Arterial stenosis                   | 1                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|                    | Arterial thrombosis                 | 8                                                                       | 14         | 1           | 1          | 15                | 0                                                              | 0          |
|                    | Arteriosclerosis                    | 30                                                                      | 49         | 3           | 6          | 55                | 0                                                              | 0          |
|                    | Arteriovenous fistula               | 2                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |

|          |                                        | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|----------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                        | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                     | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Arteritis                              | 3                                                                       | 3          | 1           | 1          | 4                 | 0                                                              | 0          |
|          | Artery dissection                      | 8                                                                       | 11         | 0           | 0          | 11                | 0                                                              | 0          |
|          | Axillary vein thrombosis               | 5                                                                       | 9          | 0           | 2          | 11                | 0                                                              | 0          |
|          | Behcet's syndrome                      | 3                                                                       | 7          | 0           | 2          | 9                 | 0                                                              | 0          |
|          | Blood pressure fluctuation             | 26                                                                      | 53         | 49          | 162        | 215               | 0                                                              | 0          |
|          | Blood pressure inadequately controlled | 1                                                                       | 3          | 3           | 7          | 10                | 0                                                              | 0          |
|          | Bloody discharge                       | 3                                                                       | 5          | 8           | 16         | 21                | 0                                                              | 0          |
|          | Blue toe syndrome                      | 3                                                                       | 4          | 2           | 11         | 15                | 0                                                              | 0          |
|          | Brachiocephalic artery occlusion       | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Brachiocephalic vein thrombosis        | 3                                                                       | 6          | 1           | 1          | 7                 | 0                                                              | 0          |
|          | Capillary disorder                     | 1                                                                       | 1          | 4           | 6          | 7                 | 0                                                              | 0          |
|          | Capillary fragility                    | 3                                                                       | 4          | 8           | 17         | 21                | 0                                                              | 0          |
|          | Capillary leak syndrome                | 5                                                                       | 7          | 0           | 0          | 7                 | 0                                                              | 0          |
|          | Carotidynia                            | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Circulatory collapse                   | 129                                                                     | 148        | 14          | 15         | 163               | 0                                                              | 0          |
|          | Claudication of jaw muscles            | 1                                                                       | 1          | 1           | 2          | 3                 | 0                                                              | 0          |
|          | Collateral circulation                 | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Cryoglobulinaemia                      | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Cyanosis                               | 52                                                                      | 98         | 52          | 158        | 256               | 0                                                              | 0          |
|          | Deep vein thrombosis                   | 673                                                                     | 1299       | 34          | 42         | 1341              | 0                                                              | 0          |
|          | Dialysis hypotension                   | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Diastolic hypertension                 | 1                                                                       | 2          | 1           | 1          | 3                 | 0                                                              | 0          |
|          | Distributive shock                     | 1                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Dry gangrene                           | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Embolism                               | 21                                                                      | 34         | 0           | 0          | 34                | 0                                                              | 0          |
|          | Embolism arterial                      | 6                                                                       | 11         | 0           | 0          | 11                | 0                                                              | 0          |
|          | Embolism venous                        | 14                                                                      | 24         | 0           | 0          | 24                | 0                                                              | 0          |
|          | Endothelial dysfunction                | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Erythromelalgia                        | 3                                                                       | 3          | 2           | 3          | 6                 | 0                                                              | 0          |
|          | Essential hypertension                 | 8                                                                       | 16         | 2           | 8          | 24                | 0                                                              | 0          |
|          | Extravasation blood                    | 2                                                                       | 3          | 2           | 4          | 7                 | 0                                                              | 0          |
|          | Extremity necrosis                     | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Femoral artery embolism                | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Fibromuscular dysplasia                | 0                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Flushing                               | 78                                                                      | 173        | 406         | 2815       | 2988              | 0                                                              | 0          |
|          | Giant cell arteritis                   | 25                                                                      | 34         | 5           | 15         | 49                | 0                                                              | 0          |
|          | Granulomatosis with polyangiitis       | 5                                                                       | 6          | 0           | 0          | 6                 | 0                                                              | 0          |
|          | Haematoma                              | 66                                                                      | 96         | 285         | 399        | 495               | 0                                                              | 0          |
|          | Haemodynamic instability               | 4                                                                       | 7          | 0           | 0          | 7                 | 0                                                              | 0          |
|          | Haemorrhage                            | 231                                                                     | 440        | 50          | 78         | 518               | 0                                                              | 0          |
|          | Haemorrhagic infarction                | 2                                                                       | 4          | 0           | 0          | 4                 | 0                                                              | 0          |
|          | Haemorrhagic vasculitis                | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Hot flush                              | 233                                                                     | 284        | 676         | 1745       | 2029              | 0                                                              | 0          |
|          | Hyperaemia                             | 5                                                                       | 5          | 5           | 10         | 15                | 0                                                              | 0          |
|          | Hypertension                           | 507                                                                     | 902        | 631         | 2123       | 3025              | 0                                                              | 0          |
|          | Hypertension neonatal                  | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Hypertensive crisis                    | 87                                                                      | 176        | 8           | 9          | 185               | 0                                                              | 0          |
|          | Hypertensive emergency                 | 14                                                                      | 27         | 0           | 0          | 27                | 0                                                              | 0          |
|          | Hypertensive urgency                   | 2                                                                       | 18         | 0           | 0          | 18                | 0                                                              | 0          |

|          |                                       | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|---------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                       | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                    | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Hypoperfusion                         | 2                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Hypotension                           | 339                                                                     | 663        | 347         | 1077       | 1740              | 0                                                              | 0          |
|          | Hypotensive crisis                    | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Hypovolaemic shock                    | 4                                                                       | 11         | 0           | 0          | 11                | 0                                                              | 0          |
|          | Iliac artery arteriosclerosis         | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Iliac artery embolism                 | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Iliac artery occlusion                | 4                                                                       | 7          | 0           | 0          | 7                 | 0                                                              | 0          |
|          | Iliac artery stenosis                 | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Iliac vein stenosis                   | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Infarction                            | 14                                                                      | 25         | 0           | 0          | 25                | 0                                                              | 0          |
|          | Inferior vena cava dilatation         | 6                                                                       | 7          | 0           | 0          | 7                 | 0                                                              | 0          |
|          | Intermittent claudication             | 5                                                                       | 8          | 0           | 1          | 9                 | 0                                                              | 0          |
|          | Internal haemorrhage                  | 28                                                                      | 47         | 0           | 1          | 48                | 0                                                              | 0          |
|          | Ischaemia                             | 30                                                                      | 40         | 0           | 2          | 42                | 0                                                              | 0          |
|          | Ischaemic limb pain                   | 1                                                                       | 1          | 1           | 1          | 2                 | 0                                                              | 0          |
|          | Jugular vein distension               | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Jugular vein embolism                 | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Jugular vein occlusion                | 1                                                                       | 5          | 1           | 1          | 6                 | 0                                                              | 0          |
|          | Jugular vein thrombosis               | 16                                                                      | 28         | 0           | 1          | 29                | 0                                                              | 0          |
|          | Kawasaki's disease                    | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Labile blood pressure                 | 3                                                                       | 4          | 17          | 19         | 23                | 0                                                              | 0          |
|          | Labile hypertension                   | 1                                                                       | 2          | 2           | 4          | 6                 | 0                                                              | 0          |
|          | Leriche syndrome                      | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Lower limb artery perforation         | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Lymphoedema                           | 36                                                                      | 46         | 37          | 100        | 146               | 0                                                              | 0          |
|          | Lymphorrhoea                          | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Lymphostasis                          | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Malignant hypertension                | 2                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | May-Thurner syndrome                  | 0                                                                       | 4          | 1           | 1          | 5                 | 0                                                              | 0          |
|          | Microangiopathy                       | 2                                                                       | 2          | 1           | 2          | 4                 | 0                                                              | 0          |
|          | Microembolism                         | 4                                                                       | 6          | 0           | 0          | 6                 | 0                                                              | 0          |
|          | Microscopic polyangiitis              | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Necrosis ischaemic                    | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Neurogenic shock                      | 6                                                                       | 6          | 4           | 4          | 10                | 0                                                              | 0          |
|          | Obstructive shock                     | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Orthostatic hypertension              | 0                                                                       | 1          | 0           | 3          | 4                 | 0                                                              | 0          |
|          | Orthostatic hypotension               | 15                                                                      | 31         | 22          | 57         | 88                | 0                                                              | 0          |
|          | Paget-Schroetter syndrome             | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Pallor                                | 90                                                                      | 152        | 234         | 1271       | 1423              | 0                                                              | 0          |
|          | Paradoxical embolism                  | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Pelvic venous thrombosis              | 7                                                                       | 15         | 0           | 0          | 15                | 0                                                              | 0          |
|          | Penetrating aortic ulcer              | 2                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Peripheral arterial occlusive disease | 3                                                                       | 8          | 3           | 5          | 13                | 0                                                              | 0          |
|          | Peripheral artery aneurysm            | 1                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Peripheral artery occlusion           | 6                                                                       | 14         | 0           | 0          | 14                | 0                                                              | 0          |
|          | Peripheral artery stenosis            | 2                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Peripheral artery thrombosis          | 18                                                                      | 42         | 2           | 2          | 44                | 0                                                              | 0          |
|          | Peripheral circulatory failure        | 5                                                                       | 8          | 13          | 16         | 24                | 0                                                              | 0          |
|          | Peripheral coldness                   | 128                                                                     | 164        | 195         | 689        | 853               | 0                                                              | 0          |

|          |                                      | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|--------------------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                                      | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                                   | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Peripheral embolism                  | 6                                                                       | 12         | 2           | 2          | 14                | 0                                                              | 0          |
|          | Peripheral ischaemia                 | 11                                                                      | 22         | 5           | 5          | 27                | 0                                                              | 0          |
|          | Peripheral vascular disorder         | 9                                                                       | 12         | 64          | 94         | 106               | 0                                                              | 0          |
|          | Peripheral vein occlusion            | 2                                                                       | 5          | 1           | 1          | 6                 | 0                                                              | 0          |
|          | Peripheral vein stenosis             | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Peripheral vein thrombus extension   | 1                                                                       | 5          | 0           | 0          | 5                 | 0                                                              | 0          |
|          | Peripheral venous disease            | 10                                                                      | 12         | 11          | 13         | 25                | 0                                                              | 0          |
|          | Periphlebitis                        | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Phlebitis                            | 17                                                                      | 23         | 27          | 51         | 74                | 0                                                              | 0          |
|          | Phlebitis deep                       | 1                                                                       | 1          | 1           | 2          | 3                 | 0                                                              | 0          |
|          | Phlebitis superficial                | 3                                                                       | 6          | 5           | 6          | 12                | 0                                                              | 0          |
|          | Polyarteritis nodosa                 | 3                                                                       | 3          | 0           | 0          | 3                 | 0                                                              | 0          |
|          | Poor peripheral circulation          | 7                                                                       | 13         | 10          | 28         | 41                | 0                                                              | 0          |
|          | Popliteal artery entrapment syndrome | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Post thrombotic syndrome             | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Prehypertension                      | 0                                                                       | 1          | 0           | 1          | 2                 | 0                                                              | 0          |
|          | Raynaud's phenomenon                 | 5                                                                       | 13         | 21          | 62         | 75                | 0                                                              | 0          |
|          | Secondary hypertension               | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Shock                                | 47                                                                      | 84         | 0           | 1          | 85                | 0                                                              | 0          |
|          | Shock haemorrhagic                   | 5                                                                       | 11         | 0           | 0          | 11                | 0                                                              | 0          |
|          | Shock symptom                        | 2                                                                       | 7          | 0           | 2          | 9                 | 0                                                              | 0          |
|          | Spider vein                          | 0                                                                       | 1          | 9           | 13         | 14                | 0                                                              | 0          |
|          | Subclavian artery embolism           | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Subclavian artery occlusion          | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Subclavian artery thrombosis         | 0                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Subclavian vein occlusion            | 0                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | Subclavian vein thrombosis           | 13                                                                      | 22         | 0           | 0          | 22                | 0                                                              | 0          |
|          | Superficial vein prominence          | 1                                                                       | 1          | 6           | 15         | 16                | 0                                                              | 0          |
|          | Superficial vein thrombosis          | 42                                                                      | 75         | 54          | 101        | 176               | 0                                                              | 0          |
|          | Susac's syndrome                     | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Systolic hypertension                | 0                                                                       | 3          | 1           | 2          | 5                 | 0                                                              | 0          |
|          | Thrombophlebitis                     | 28                                                                      | 39         | 37          | 62         | 101               | 0                                                              | 0          |
|          | Thrombophlebitis migrans             | 1                                                                       | 1          | 0           | 0          | 1                 | 0                                                              | 0          |
|          | Thrombosed varicose vein             | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Thrombosis                           | 781                                                                     | 1403       | 80          | 115        | 1518              | 0                                                              | 0          |
|          | Varicophlebitis                      | 2                                                                       | 4          | 3           | 5          | 9                 | 0                                                              | 0          |
|          | Varicose vein                        | 9                                                                       | 13         | 37          | 69         | 82                | 0                                                              | 0          |
|          | Varicose vein ruptured               | 0                                                                       | 0          | 2           | 2          | 2                 | 0                                                              | 0          |
|          | Vascular calcification               | 4                                                                       | 6          | 1           | 1          | 7                 | 0                                                              | 0          |
|          | Vascular compression                 | 0                                                                       | 0          | 0           | 2          | 2                 | 0                                                              | 0          |
|          | Vascular insufficiency               | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Vascular occlusion                   | 5                                                                       | 7          | 0           | 1          | 8                 | 0                                                              | 0          |
|          | Vascular pain                        | 14                                                                      | 16         | 30          | 50         | 66                | 0                                                              | 0          |
|          | Vascular rupture                     | 2                                                                       | 6          | 3           | 4          | 10                | 0                                                              | 0          |
|          | Vascular wall discolouration         | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Vasculitis                           | 42                                                                      | 64         | 29          | 59         | 123               | 0                                                              | 0          |
|          | Vasculitis necrotising               | 1                                                                       | 2          | 1           | 1          | 3                 | 0                                                              | 0          |
|          | Vasoconstriction                     | 1                                                                       | 1          | 2           | 7          | 8                 | 0                                                              | 0          |
|          | Vasodilatation                       | 10                                                                      | 10         | 39          | 72         | 82                | 0                                                              | 0          |

|          |                         | Spontaneous, including competent authorities (worldwide) and literature |            |             |            | Total Spontaneous | Non-interventional post-marketing study and reports from other |            |
|----------|-------------------------|-------------------------------------------------------------------------|------------|-------------|------------|-------------------|----------------------------------------------------------------|------------|
|          |                         | Serious                                                                 |            | Non-Serious |            |                   | Serious                                                        |            |
| SOC_TERM | PT                      | Interval                                                                | Cumulative | Interval    | Cumulative | Cumulative All    | Interval                                                       | Cumulative |
|          | Vasospasm               | 1                                                                       | 2          | 3           | 4          | 6                 | 0                                                              | 0          |
|          | Vein collapse           | 1                                                                       | 2          | 1           | 2          | 4                 | 0                                                              | 0          |
|          | Vein discolouration     | 3                                                                       | 4          | 2           | 15         | 19                | 0                                                              | 0          |
|          | Vein disorder           | 3                                                                       | 4          | 14          | 36         | 40                | 0                                                              | 0          |
|          | Vein rupture            | 6                                                                       | 11         | 4           | 4          | 15                | 0                                                              | 0          |
|          | Vena cava thrombosis    | 5                                                                       | 15         | 0           | 0          | 15                | 0                                                              | 0          |
|          | Venous aneurysm         | 0                                                                       | 0          | 0           | 1          | 1                 | 0                                                              | 0          |
|          | Venous haemorrhage      | 2                                                                       | 2          | 1           | 1          | 3                 | 0                                                              | 0          |
|          | Venous occlusion        | 6                                                                       | 11         | 0           | 1          | 12                | 0                                                              | 0          |
|          | Venous thrombosis       | 39                                                                      | 60         | 8           | 13         | 73                | 0                                                              | 0          |
|          | Venous thrombosis limb  | 47                                                                      | 68         | 10          | 17         | 85                | 0                                                              | 0          |
|          | Vessel perforation      | 0                                                                       | 0          | 1           | 1          | 1                 | 0                                                              | 0          |
|          | Visceral congestion     | 1                                                                       | 2          | 0           | 0          | 2                 | 0                                                              | 0          |
|          | White coat hypertension | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
|          | Withdrawal hypertension | 0                                                                       | 0          | 1           | 2          | 2                 | 0                                                              | 0          |
| [Total]  |                         | 196190                                                                  | 287616     | 518254      | 1360254    | 1647870           | 13                                                             | 18         |



## **20.4.      Appendix 4      Tabular Summary of Safety Signals**

**20.4.1. Appendix 4a Tabular summary of safety signals new, ongoing or closed during the reporting interval mRNA-1273**

Reporting interval: 01 Jul 2021 to 31 Dec 2021

**Table 20.1 Tabular summary of safety signals new, ongoing or closed during the reporting interval**

| Signal term | Date detected | Status (new, ongoing or closed) | Date closed (for closed signals) | Source of trigger of signal    | Reason for Evaluation and summary of key data                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Method of signal evaluation | Action(s) taken or planned    |
|-------------|---------------|---------------------------------|----------------------------------|--------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|-------------------------------|
| Dizziness   | 21-May-2021   | Closed                          | 28 Jul 2021                      | Health Authority/P RAC request | This signal arose from signal detection of UK adverse drug reaction (ADR) reports (MHRA request -MSSR#3). Whilst the majority of patients appear to have experienced dizziness the same day as vaccination, there are also cases whereby the patient has experienced dizziness with a longer onset time. Whilst the term dizziness encompasses a range of symptoms, there are broad categories of dizziness that include, but may not be limited to: 1) Feeling faint, which often occurs shortly after vaccination 2) Dizziness associated with reactogenicity 3) Dizziness secondary to a vestibular, inner-ear cause, MHRA requests that the current cases of dizziness are reviewed by Moderna, to determine if this term should be included in the SmPC. MHRA also stated that, this signal should also be explored if a neurological cause may be associated with the dizziness cases, and whether any cases pose a risk to driving or operating machinery.<br>Review of clinical trial data showed minimal imbalance between placebo (4) and mRNA-1273 (17) P301 study cohorts especially Day | Signal Evaluation Report    | Update RSI (CCDS, local SmPC) |

| Signal term          | Date detected | Status (new, ongoing or closed) | Date closed (for closed signals) | Source of trigger of signal    | Reason for Evaluation and summary of key data                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Method of signal evaluation    | Action(s) taken or planned               |
|----------------------|---------------|---------------------------------|----------------------------------|--------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------|------------------------------------------|
|                      |               |                                 |                                  |                                | 1 to 7 after second injection. Observed to expected analyses showed reporting rates below the background rates. In the spontaneous reports setting, dizziness was 11th most frequently reported adverse event in Moderna (mRNA-1273) global safety database. TTO was usually within 1-7 days suggesting vasovagal or reactogenicity-related events. Insufficient evidence was found for vertigo, vertigo positional, tinnitus, fall and road traffic accidents in the context of dizziness, with no important imbalances noted. Based on available data and biological plausibility based on known reactogenicity and vasovagal reactions following mRNA-1273 injection, MAH considered dizziness as an identified risk (not important). SPIKVAX CCDS will be updated. |                                |                                          |
| Neuralgic Amyotrophy | 17-Jun-2021   | Closed                          | 08 Jul 2021                      | Health Authority/P RAC request | Trigger: Swissmedic Request for Safety Assessment of Neuralgic amyotrophy, 15 Jun 2021<br>Summary of results: Based on the analysis of all the safety data available as of 31 May 2021, the MAH considers that Neuralgic amyotrophy, Radiculitis brachial, and Brachial plexus injury are not presently a safety issue of concern. A total of 28 case reports with the PTs of Neuralgic amyotrophy, Radiculitis brachial, and Brachial plexus injury were identified worldwide (including one report of neuralgic amyotrophy reported in 4.1(b) ) in the MAH global safety database. Six out of the 28 cases (21.4%) were considered serious reports. When calculating                                                                                                 | Response to Health Authorities | Monitoring via Routine Pharmacovigilance |

| Signal term         | Date detected | Status (new, ongoing or closed) | Date closed (for closed signals) | Source of trigger of signal    | Reason for Evaluation and summary of key data                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Method of signal evaluation    | Action(s) taken or planned               |
|---------------------|---------------|---------------------------------|----------------------------------|--------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------|------------------------------------------|
|                     |               |                                 |                                  |                                | person-time on the basis of a 21-day risk window following each globally administered dose as of 31 May 2021, the observed reporting rate for neuralgic amyotrophy was 0.30 cases per 100,000 person years, which fell below expected rates. The MAH will continue to closely evaluate events of Neuralgic amyotrophy, Radiculitis brachial, and Brachial plexus injury using routine surveillance. Swiss medic has reviewed Company response on neuralgic amyotrophy and hence closed the signal.                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                |                                          |
| Erythema Multiforme | 23 Jul 2021   | Closed                          | 24-Aug-2021                      | Health Authority/P RAC request | Signal assessment report (EPITT no 19720) received from PRAC on 23/Jul/2021 requesting the MAH (Moderna) to provide a cumulative review of erythema multiforme based on data from all available sources using the PT Erythema multiforme and including cases from clinical trial, spontaneous sources and literature. Based on the review of all available sources, no cases of erythema multiforme (EM) were reported in the clinical setting. In the Company global safety database 29 confirmed case reports of EM were reported (26 in females / 12 in males / 1 unknown). Based on the EMA / WHO case definition, 22 cases were categorized as EM minor and 7 as EM major. Most cases had possible risk factors for EM such as herpes simplex virus (principal risk factor for EM), drug hypersensitivity, allergies, immunosuppressive conditions such as diabetes mellitus, corticosteroid therapy, cancer chemotherapy etc. and drugs associated | Response to Health Authorities | Monitoring via Routine Pharmacovigilance |

| Signal term                               | Date detected | Status (new, ongoing or closed) | Date closed (for closed signals) | Source of trigger of signal    | Reason for Evaluation and summary of key data                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Method of signal evaluation    | Action(s) taken or planned               |
|-------------------------------------------|---------------|---------------------------------|----------------------------------|--------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------|------------------------------------------|
|                                           |               |                                 |                                  |                                | with EM such as antibiotics (e.g. cephalosporins, macrolides, sulfonamides), antipyretics, antidepressants, and seizure medicines. Most case reports occurred after the first dose (of the 29 confirmed cases 4 occurred after dose 2), with a TTO suggestive of reactogenicity (initial peak which dropped and plateaued at baseline) rather than a delayed hypersensitivity reaction. The O/E analysis based on the 29 confirmed EM cases showed no increase in the observed vs the expected rate. Literature review retrieved a few case reports of EM in temporal association with mRNA vaccines or with COVID-19 infection itself, including multifactorial risk factors. In conclusion MAH considered EM in association with SPIKVAX as a refuted signal, due to the lack of evidence across data sources reviewed. MAH did not plan to update the product information and/or risk management plan, including relevant risk minimization measures. EM will be monitored through routine PV surveillance (PRAC recommendation expected 27-30 Sep 2021) |                                |                                          |
| Glomerulonephritis and nephrotic syndrome | 23 Jul 2021   | Closed                          | 24-Aug-2021                      | Health Authority/P RAC request | Signal assessment report (EPITT 19724) on glomerulonephritis and nephrotic syndrome was received from PRAC on 23/Jul/2021 requesting the MAH to provide a cumulative review of glomerulonephritis and nephrotic syndrome from all available sources using HLT Glomerulonephritis and nephrotic syndrome to include cases of IgA nephropathy (glomerulonephritis) and minimal change disease (nephrotic syndrome) and related                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Response to Health Authorities | Monitoring via Routine Pharmacovigilance |

| Signal term | Date detected | Status (new, ongoing or closed) | Date closed (for closed signals) | Source of trigger of signal | Reason for Evaluation and summary of key data                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Method of signal evaluation | Action(s) taken or planned |
|-------------|---------------|---------------------------------|----------------------------------|-----------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|----------------------------|
|             |               |                                 |                                  |                             | <p>terms. Based on the review of all available sources, no cases of glomerulonephritis (GN) or nephrotic syndrome (NS) were reported in the clinical setting. In the Company global safety database 33 cases of GN and NS were reported. Sixteen were hospitalized. Three patients were reported to have renal failure: one patient had an exacerbation of pre-existing disease, one patient had de novo disease, and for one patient the information was not reported. One additional patient with de novo disease was treated with dialysis. There were no deaths reported. IgA nephropathy was the most common glomerulonephritis PT reported, no clear pattern by Dose number and TTO patterns were not suggestive of a potential association with SPIKEVAX. O/E analyses were performed on the 24 cases where the diagnosis was not pre-existing given that background rate estimate describe incidence rather than prevalence. No analysis showed a reporting rate that exceeded the expected. Literature articles proposing mechanisms for mRNA vaccines against Covid-19 disease raise some interesting possibilities that might be addressable in future studies, however definitive conclusions cannot be drawn from them at this time. In conclusion MAH considered GN and NS in association with SPIKEVAX as a refuted signal, due to the lack of evidence across data sources reviewed. MAH did not plan to update the product information and/or risk management plan.</p> |                             |                            |

| Signal term          | Date detected | Status (new, ongoing or closed) | Date closed (for closed signals) | Source of trigger of signal                                    | Reason for Evaluation and summary of key data                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Method of signal evaluation | Action(s) taken or planned               |
|----------------------|---------------|---------------------------------|----------------------------------|----------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|------------------------------------------|
|                      |               |                                 |                                  |                                                                | including relevant risk minimization measures. GN and NS will be monitored through routine PV surveillance. Upon PRAC recommendation (dated 30 Sep 2021), MAH will closely monitor the issue of “glomerulonephritis/nephrotic syndrome, including exacerbations, and present a cumulative review of cases from all sources and relevant literature in the upcoming PSUR submissions”.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                             |                                          |
| Serious Hypertension | 6-May-2021    | Closed                          | 10-Sep-2021                      | Health Authority/PRAC request; EudraVigilance; Other (Specify) | Signal was triggered from a disproportionate reporting of Hypertensive crisis from EVDAS and a PRAC request (MSSR#3 Assessment Report dated 04/May/2021) to provide in next PSUR a cumulative review of serious hypertension (SMQ Hypertension), from all available sources (preliminary analyses presented in PBRER#1). Based on the review of all available sources, no evidence was found from no nonclinical data to support a direct effect of mRNA-1273 or SM-102, the small molecule lipid used in the LNP formulation of mRNA-1273, on blood pressure. While there has been proposed a theoretical mechanistic link between systemic spike protein and renin-angiotensin system which could lead to increases in BP, this causal association in non-clinical studies has not been demonstrated. In the MAH global safety database, there was a temporal association of serious hypertension with SPIKEVAX administration, particularly for the first few days after the first dose of SPIKEVAX. This could be explained by the | Signal Evaluation Report    | Monitoring via Routine Pharmacovigilance |



| Signal term                       | Date detected | Status (new, ongoing or closed) | Date closed (for closed signals) | Source of trigger of signal    | Reason for Evaluation and summary of key data                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Method of signal evaluation    | Action(s) taken or planned                                         |
|-----------------------------------|---------------|---------------------------------|----------------------------------|--------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------|--------------------------------------------------------------------|
|                                   |               |                                 |                                  |                                | acute stress/anxiety/pain response or as a secondary symptom from reactogenicity symptoms or the inflammatory response associated with vaccination. In addition, the cases occurred more frequently in females than males which differed from the baseline tendency for a higher risk of hypertension in males. However, white coat hypertension has been reported to have a stronger association with female gender. Most serious hypertension occurred in older patients, many of whom had multiple cardiovascular risk factors or concurrent events that could directly or indirectly contribute to elevated blood pressure. The O/E analyses showed observed rates well below background incidence rates. There was limited evidence in the literature supporting a potential causal association between hypertension and mRNA COVID-19 vaccination. In conclusion MAH, considered serious hypertension in association with as a refuted. No changes are required to current weekly signal detection process, clinical trial conduct, labelling, other reference safety information or the risk management plan. Events of serious hypertension will continue to be monitored through routine pharmacovigilance activities. |                                |                                                                    |
| Multisystem Inflammatory Syndrome | 3-Sep-2021    | Closed                          | 28-Sep-2021                      | Health Authority/P RAC request | PRAC Signal Assessment (EPITT 19732) was received on 03/Sep/2021 requesting MAHs for Covid-19 vaccines (including Spikevax) to perform a cumulative review of Multisystem Inflammatory Syndrome (MIS), following receipt of one well-described case in a child                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Response to Health Authorities | Close Monitoring: Additional Risk Minimization Measures (Specify); |



| Signal term | Date detected | Status (new, ongoing or closed) | Date closed (for closed signals) | Source of trigger of signal | Reason for Evaluation and summary of key data                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Method of signal evaluation | Action(s) taken or planned               |
|-------------|---------------|---------------------------------|----------------------------------|-----------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|------------------------------------------|
|             |               |                                 |                                  |                             | who experienced multisystem inflammatory syndrome in children (MIS-C) after vaccination with COVID-19 mRNA vaccine (nucleoside-modified) Comirnaty. The review should present both cases of MIS-C and cases of multisystem inflammatory syndrome in adults (MIS-A). The cases should be identified using at least the following list of terms: multisystem inflammatory syndrome in children, systemic inflammatory response syndrome, multiple organ dysfunction syndrome, Kawasaki's disease, toxic shock syndrome, distributive shock, hypotensive crisis, vaccine associated enhanced disease, vaccine associated enhanced respiratory disease, cytokine release syndrome, cytokine storm, haemophagocytic lymphohistiocytosis, macrophage activation, macrophages increased, septic shock, autoinflammatory disease. The Brighton Collaboration case definition should be used, including for the age range of MIS-C (<21 years of age). Based on the review of all available sources, using a broad list of preferred terms to retrieve potential MIS reports, 4 cases were reported in the CT setting, none of which were considered as related to mRNA-1273. From the Company global safety database out of a total of 197 case reports (including 3 cases below 21 years of age), 3 reports were classified as Brighton Collaboration Level 2b of diagnostic certainty based on very limited information (2 conditional /1 possible). Majority of the reports were heavily confounded due to the |                             | Monitoring via Routine Pharmacovigilance |

| Signal term         | Date detected | Status (new, ongoing or closed) | Date closed (for closed signals) | Source of trigger of signal         | Reason for Evaluation and summary of key data                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Method of signal evaluation | Action(s) taken or planned               |
|---------------------|---------------|---------------------------------|----------------------------------|-------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|------------------------------------------|
|                     |               |                                 |                                  |                                     | reported events including septic shock, sepsis, acute respiratory distress, associated COVID-19 pneumonia, Haemophagocytic lymphohistiocytosis (19 cases), cytokine storm related events right after vaccination. All these are considered differential diagnosis conditions. The O/E analysis based a more specific MedDRA case definition showed no increase in the observed vs the expected rates. A few articles on MIS in children following vaccination were retrieved, however their review did not provide sufficient evidence to support a potential causal association. In conclusion MAH considered MIS in association with SPIKEVAX as a refuted signal, due to the lack of evidence across data sources reviewed. MAH did not plan to update the product information and/or risk management plan, including relevant risk minimization measures. MIS will be monitored through routine PV surveillance. Following feedback from the health authorities on 28/Oct/2021, a Follow-Up questionnaire for MIS was implemented. |                             |                                          |
| Myelitis Transverse | 23-Aug-2021   | Closed                          | 08 Oct 2021                      | Literature Article; Other (Specify) | The signal was triggered following review of an article 'Sudden onset of myelitis after COVID-19 vaccination' (ref. W F. Fitzsimmons W and Nance CS. Sudden Onset of Myelitis after COVID-19 Vaccination: An Under-Recognized Severe Rare Adverse Event (May 5, 2021) in the frame of PBRER#1. Following assessment based on the review of all available sources, no cases of transverse myelitis (TM) were reported in the                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Signal Evaluation Report    | Monitoring via Routine Pharmacovigilance |

| Signal term | Date detected | Status (new, ongoing or closed) | Date closed (for closed signals) | Source of trigger of signal | Reason for Evaluation and summary of key data                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Method of signal evaluation | Action(s) taken or planned |
|-------------|---------------|---------------------------------|----------------------------------|-----------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|----------------------------|
|             |               |                                 |                                  |                             | CT setting. From the Company global safety database out of a total of 76 case reports (median age 60y, ranged from 22Y to 88Y), 33 reports were classified as possible Brighton Collaboration Level2/2A/3 of diagnostic certainty. Majority of reports included confounding / risk factors, such as hypertension, diabetes mellitus, gastroesophageal reflux disease, hyperlipidemia, tobacco use, connective tissue / autoimmune diseases, mixed connective tissue disease, systemic sclerosis, urticarial vasculitis, thyroid disease, nutritional deficiency (vitamin B12, vitamin E; copper) and recently COVID-19 infection, use of aspirin and statins. The O/E analysis showed observed counts higher than expected in older males (65 and older), however the point estimates were not statistically significant and were based on small counts for age-stratified analyses. A few articles described TM following vaccination with mRNA vaccine, however none provided sufficient evidence to support a potential causal association. In conclusion MAH considered TM in association with SPIKEVAX as a refuted signal, due to the lack of evidence across data sources reviewed. MAH did not plan to update the product information and/or risk management plan, including relevant risk minimization measures. TM will continue to be monitored through routine PV surveillance, including weekly signal detection activities. |                             |                            |

| Signal term             | Date detected | Status (new, ongoing or closed) | Date closed (for closed signals) | Source of trigger of signal    | Reason for Evaluation and summary of key data                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Method of signal evaluation                               | Action(s) taken or planned               |
|-------------------------|---------------|---------------------------------|----------------------------------|--------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------|------------------------------------------|
| Capillary Leak Syndrome | 28 Oct 2021   | Closed                          | 15-Nov-2021                      | Health Authority/P RAC request | <p>PRAC, in their signal assessment report (EPITT ref. No. 19743) (28/Oct/2021), following consideration of the available evidence from the on-going monitoring of this safety topic in the MSSRs and the new case reports from a national database in Italy, requested an updated analysis of the association between SPIKEVAX and capillary leak syndrome (CLS) from all available sources.</p> <p>Following assessment based on the review of all available sources, no cases of capillary leak syndrome (CLS) were reported in the CT setting. Strength of association was weak from the 8 cases retrieved from the Company global safety database: 4 cases were assessed as possibly related (including 2 cases with no other information than a temporal association). No influence on CLS reporting with SPIKEVAX (due to notoriety bias) following inclusion of CLS in other Covid-19 vaccines labels (Vaxzevria and Janssen). Low reporting rate and stability over time (0.09/1mio doses administered or 0.03 per 100,000 patient-years). No disproportionate reporting in EVDAS or VAERS. The O/E analysis did not provide observed counts higher than expected. In age-stratified O/E analysis interpretability of data was limited due to small numbers. Several articles described CLS and mRNA vaccine, but none showed a direct temporal association with mRNA vaccines against Covid-19 disease. No plausible pathognomonic findings were found</p> | Response to Health Authorities ; Signal Evaluation Report | Monitoring via Routine Pharmacovigilance |

| Signal term                      | Date detected | Status (new, ongoing or closed) | Date closed (for closed signals) | Source of trigger of signal                     | Reason for Evaluation and summary of key data                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Method of signal evaluation                               | Action(s) taken or planned               |
|----------------------------------|---------------|---------------------------------|----------------------------------|-------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------|------------------------------------------|
|                                  |               |                                 |                                  |                                                 | to support a possible causal association between the administration of SPIKEVAX and the occurrence of CLS or flare-up. In conclusion MAH considered CLS in association with SPIKEVAX as a refuted signal, due to the lack of evidence across data sources reviewed. MAH did not plan to update the product information and/or risk management plan, including relevant risk minimization measures. CLS will continue to be monitored through routine PV surveillance.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                           |                                          |
| Cerebral Venous Sinus Thrombosis | 1-Dec-2021    | Closed                          | 20-Dec-2021                      | Health Authority/P RAC request; Other (Specify) | <p>The signal of Central venous sinus thrombosis (CVST) was triggered from a signal assessment request from Swissmedic (letter dated 26/Nov/2021).</p> <p>Following assessment, based on the review of all available sources, no cases of CVST were reported in the CT setting. 72 out of a total of 122 cases met a Brighton Collaboration Case level 1,2 or 3 definitions? No cases were assessed with a certain or probable WHO causality. 62% of cases were assessed with a possible, mostly because of temporal association. Most of the CVST cases had risk factors known for CVST, such as oral contraceptive use, drug hypersensitivity, history of thrombotic events, hypertension, diabetes, hyperlipidemia. No unique or novel risk factors were identified from this small aggregate sample. No evidence to support a causal hypothesis/ association was found from the literature review. Observed to Expected ratio: very rare event without significant disproportionality.</p> | Response to Health Authorities ; Signal Evaluation Report | Monitoring via Routine Pharmacovigilance |

| Signal term           | Date detected | Status (new, ongoing or closed) | Date closed (for closed signals) | Source of trigger of signal    | Reason for Evaluation and summary of key data                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Method of signal evaluation    | Action(s) taken or planned |
|-----------------------|---------------|---------------------------------|----------------------------------|--------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------|----------------------------|
|                       |               |                                 |                                  |                                | In conclusion MAH considered CVST in association with SPIKEVAX as a refuted signal, due to the lack of evidence across data sources reviewed. MAH did not plan to update the product information and/or risk management plan, including relevant risk minimization measures. CVST will continue to be monitored through routine PV surveillance.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                |                            |
| Autoimmune hepatitis* | 02-Dec-2021   | Ongoing                         | NA                               | Health Authority/P RAC request | The signal of Autoimmune hepatitis (AIH) was triggered from PRAC signal assessment report (EPITT 19750) (dated 02/Dec/2021), based on the available evidence from case reports published in the literature and submitted to Eudravigilance (EV). Following assessment based on the review of all available sources, no cases of AIH were reported in the CT setting. Analysis from the Company global safety database retrieved 165 cases, 11 cases (7%) were suggestive of AIH, and of these, 8 cases were considered as related (including cases where only temporal association with SPIKEVAX was reported). No disproportionate reporting of AIH was found in EVDAS or VAERS. The O/E analysis for PT AID did not provide observed counts higher than expected. In age-stratified O/E analysis interpretability of data was limited due to small numbers. Several articles described AIH and mRNA vaccine, but none showed a direct temporal association with mRNA vaccines against Covid-19 disease. No plausible pathognomonic findings were found to support a possible causal association between the administration of SPIKEVAX and the | Response to Health Authorities | Evaluation Ongoing         |



| Signal term                                                      | Date detected | Status (new, ongoing or closed) | Date closed (for closed signals) | Source of trigger of signal                                                                                                                                                                                    | Reason for Evaluation and summary of key data                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Method of signal evaluation                                | Action(s) taken or planned |
|------------------------------------------------------------------|---------------|---------------------------------|----------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------|----------------------------|
|                                                                  |               |                                 |                                  |                                                                                                                                                                                                                | occurrence of AIH. In conclusion MAH considered AIH in association with SPIKEVAX as a refuted signal, due to the lack of evidence across data sources reviewed. MAH did not plan to update the product information and/or risk management plan, including relevant risk minimization measures. AIH will continue to be monitored through routine PV surveillance.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                            |                            |
| Myocarditis and pericarditis (PRAC FU EPITT 19713 - Nordic data) | 14 Oct 2021   | Closed                          | 10 Dec 2021                      | HA Request, Other (PRAC Signal AR (dated 14/Oct/2021) following circulation of preliminary results dated 5th October 2021 of a study entitled "SARS-CoV-2 vaccination and risk of pericarditis and myocarditis | A signal of myocarditis and pericarditis was evaluated as an important identified risk in Jun/2021, which resulted in an update to MAH CCDS and RMP. A new signal for myocarditis and pericarditis was opened based on PRAC Signal AR (dated 14/Oct/2021) (EPITT no: 19713) following circulation of preliminary results dated 5th October 2021 of a study entitled "SARS-CoV-2 vaccination and risk of pericarditis and myocarditis: Nordic nationwide cohort study of 20 million individuals". These analyses are undertaken within a request from the Swedish government to the Swedish Medical Products Agency of in depth safety evaluation of covid-19 vaccines. [...] PRAC, in their third recommendation (dated 02/Dec/2021) having considered the available evidence from large observational studies in and outside the EEA, as well as the data provided by the MAH, agreed that the MAH for Spikevax, should update the EU SmPC Section 4.4 (further characterisation) and Section 4.8 (frequency updated to "Very rare" for both myocarditis and pericarditis, | RTQ, Other (Signal procedure by PRAC based on Nordic data) | Update RSI (CCDS, SmPC)    |

| Signal term | Date detected | Status (new, ongoing or closed) | Date closed (for closed signals) | Source of trigger of signal                                  | Reason for Evaluation and summary of key data                                                                                                                                                                                                             | Method of signal evaluation | Action(s) taken or planned |
|-------------|---------------|---------------------------------|----------------------------------|--------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|----------------------------|
|             |               |                                 |                                  | : Nordic nationwide cohort study of 20 million individuals") | additional text under "Description of selected adverse reactions).<br>Upon review of all available data, MAH decided to update the frequency of Myocarditis and pericarditis from "unknown" to "Very rare". along with additional wording in CCDS v 11.0. |                             |                            |

\*=Autoimmune hepatitis was closed (refuted), after the DLP i.e., on 19 Jan 2022



#### **20.4.2.       Appendix 4b Signal Evaluation Reports**

**20.4.2.1.            Appendix 4b1: Signal Evaluation report: Dizziness**

**Signal Evaluation Report**  
**for**  
**mRNA-1273**  
**on**  
**Dizziness and Secondary Vestibular Disorders or Vertigo**

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## List of Abbreviations

|        |                                              |
|--------|----------------------------------------------|
| ADR    | Adverse Drug Reaction                        |
| CDC    | Centers for Disease Control and Prevention   |
| CT     | Clinical Trial                               |
| DLP    | Data Lock Point                              |
| CMQ    | Customized MedDRA query                      |
| EUA    | Emergency Use Authorization                  |
| FDA    | Food and Drug Administration                 |
| HLT    | Higher Level Term                            |
| ICSR   | Individual Case Safety Report                |
| IMP    | Investigational Medicinal Product            |
| MAH    | Marketing Authorization Holder               |
| MedDRA | Medical Dictionary for Regulatory Activities |
| PT     | Preferred Term                               |
| RA     | Regulatory Authority                         |
| SD     | Signal Detection                             |
| SOC    | System Organ Class                           |
| TEAE   | Treatment-emergent adverse event             |
| VAERS  | Vaccine Adverse Event Reporting System       |

## 1 Introduction

This report presents an evaluation of the cumulative evidence for a causal association between exposure to mRNA-1273 and subsequent development of Dizziness and Dizziness associated with vestibular disorders or vertigo. The evaluation is based on all available evidence from the company safety database, literature review, and discussion on the possible mechanism.

### 1.1 Source of the Signal

The signal evaluation was requested by the Medicines and Healthcare products Regulatory Agency (MHRA). During the recent review, MHRA have identified that dizziness is not currently listed in the UK summary of product characteristics (SmPC) for COVID-19 Vaccine Moderna. This signal arose from signal detection of UK adverse drug reaction (ADR) reports. The MHRA made the following comments:

*As of 5th May 2021, the MHRA has received 85 cases of dizziness, eight cases of dizziness postural and five cases of vertigo. The MHRA is also in receipt of dizziness cases whereby the patient also experienced vestibular ADRs, such as tinnitus, ear pain, hypoacusis and deafness. Whilst the majority of patients appear to have experienced dizziness the same day as vaccination, there are also cases whereby the patient has experienced dizziness with a longer onset time. Whilst the term dizziness encompasses a range of symptoms, there are broad categories of dizziness that include, but may not be limited to:*

- *Feeling faint, which often occurs shortly after vaccination.*
- *Dizziness associated with reactogenicity.*
- *Dizziness secondary to a vestibular, inner-ear cause.*

*Whilst the current number of dizziness cases is relatively low, it is anticipated that more cases will be reported and therefore the MHRA requests that the current cases of dizziness are reviewed by Moderna, to determine if this term should be included in the SmPC. The MHRA also requests that the cause of dizziness is explored in these cases and for comment to be provided on the evidence for each category of dizziness, although in some cases it may be challenging to determine the cause. The cases of dizziness associated with vestibular disorders or vertigo should also be examined. It should also be explored if a neurological cause may be associated with the dizziness cases, and whether any cases pose a risk to driving or operating machinery. Please confirm receipt of this letter by 4th June 2021. Please do not hesitate to contact us if you have any questions. Cause of dizziness is explored in these cases and for comment to be provided on the evidence for each category*

## **2 Background**

### **2.1 Product**

The MAH has developed mRNA-1273, a novel lipid nanoparticle (LNP)-encapsulated messenger RNA (mRNA)-based vaccine against the 2019 novel coronavirus (CoV; SARS-CoV-2). mRNA-1273, the prototype COVID-19 vaccine, encodes for the full-length spike (S) glycoprotein of the Wuhan-Hu-1 strain of SARS-CoV-2, modified to introduce 2 proline residues to stabilize the S glycoprotein into a prefusion conformation (S-2P). mRNA-1273 consists of an mRNA that is manufactured with LNPs composed of 4 lipids: SM-102, cholesterol, DSPC, and PEG2000-DMG.

### **2.2 Validated Signal:**

Dizziness is a term used to describe a range of sensations, such as feeling faint, woozy, lightheaded or unsteady. Dizziness that creates the false sense that you or your surroundings are spinning or moving is called vertigo. Dizziness has many causes, including: Overheating and dehydration, Poor blood oxygenation, poor circulation or low blood pressure, Anxiety, Neurological conditions, Low blood sugar, Medications and Motion sickness. In general, Dizziness impacts ~15 to 20% of adults annually.

For purposes of this signal evaluation, Dizziness associated with mRNA-1273 treatment was analysed in two scenarios

- a. Dizziness associated with mRNA-1273 treatment along with Dizziness secondary to vertigo, which is defined by combination of multiple PTs such as, dizziness, dizziness exertional, dizziness postural, persistent postural-perceptual dizziness, procedural dizziness, vertigo, vertigo CNS origin, and vertigo positional. All these PTs are used through a Medical Dictionary for Regulatory Activities (MedDRA) as a customized MedDRA query (CMQ), hereafter referred as Dizziness CMQ query.
- b. Dizziness associated with Tinnitus (Vestibular Disorders)

### 3 Review of Data from All Sources

The analysis of Dizziness is performed to determine Dizziness CMQ association with the use of mRNA-1273 treatment and Dizziness secondary to Tinnitus (Vestibular Disorders) was performed using several data sources. The methods of evaluation used in each of the analysed data sources is described below.

#### 3.1 Clinical Trial Data

The topic of Dizziness CMQ was cumulatively reviewed in the MAH safety database with a data-lock point (DLP) of 25 November 2020, queried with CMQ of Dizziness in P301 study. All clinical trial adverse event data was reviewed from mRNA-1273 P301 study as of the DLP 25 November 2020. Solicited adverse reactions were also reviewed. No reports of Severe Medically Attended TEAEs within 28-Days of Any Injection were observed for Dizziness. The [Table-1](#) shows the incidence of TEAEs up to 28-days after any injection.

**Table 1: Incidence of Dizziness CMQ Retrieved TEAEs up to 28-Days After any Injection**

| Preferred Term        | Placebo<br>(N=15166)<br>n (%) | mRNA-1273<br>(N=15185)<br>n (%) | Total<br>(N=30351)<br>n (%) |
|-----------------------|-------------------------------|---------------------------------|-----------------------------|
| Dizziness             | 51 (0.3)                      | 66 (0.4)                        | 117 (0.4)                   |
| Dizziness postural    | 0                             | 1 (<0.1)                        | 1 (<0.1)                    |
| Vertigo               | 16 (0.1)                      | 17 (0.1)                        | 33 (0.1)                    |
| Vertigo positional    | 1 (<0.1)                      | 6 (<0.1)                        | 7 (<0.1)                    |
| Road traffic accident | 5 (<0.1)                      | 7 (<0.1)                        | 12 (<0.1)                   |

TEAE = Treatment-emergent adverse event; P301\_Batch-1: Table 14.3.1.8.1

Form the Dizziness CMQ query, only PT of Dizziness was observed during first and second injection, of this one report of Dizziness was serious. The [Table-2](#) shows the incidence of events reported after first and second injection, with a slight increase after second injection (<0.1 vs 0.2)

**Table 2: Incidence of Dizziness CMQ Day 1 -Day 7 After First Injection**

| Preferred Term                            | Placebo<br>(N=15166)<br>n (%) | mRNA-1273<br>(N=15185)<br>n (%) | Total<br>(N=30351)<br>n (%) |
|-------------------------------------------|-------------------------------|---------------------------------|-----------------------------|
| <b>Day 1 -Day 7 After First Injection</b> |                               |                                 |                             |
| Dizziness                                 | 14 (<0.1)                     | 15 (<0.1)                       | 29 (<0.1)                   |



| Day 1 -Day 7 After Second Injection |           |          |          |
|-------------------------------------|-----------|----------|----------|
| Dizziness                           | 11 (<0.1) | 30 (0.2) | 41 (0.1) |

TEAE = Treatment-emergent adverse event; P301\_Batch-2: Table 14.3.1.8.10 and Table 14.3.1.8.11

### 3.2 Dizziness Associated with Tinnitus (Vestibular Disorders)

Tinnitus is the perceived sensation of sound--usually buzzing, hissing, or ringing--in the absence of a corresponding external acoustic stimulus. Prevalence estimated at 10%-25% of adults, but severely bothersome in less than 10%. Peak in the 7th decade of life. Prevalence of tinnitus increases with increasing hearing loss. Tinnitus can arise from pathological changes along the entire auditory pathway. The onset of tinnitus can also be associated with emotional factors and stress. In many cases tinnitus generation is multifactorial. Most widely used treatments involve counselling, and best evidence is for cognitive behavioral therapy (Langguth et al).

No Serious or severe reports of Tinnitus were reported. Tinnitus 28-day counts identical to overall with overall reports of 20 (<0.1) (PBO 11[ <0.1] vs mRNA-12739 [<0.1]).

### 3.3 Summary

Other than Dizziness (4 PBO vs 17 mRNA-1273) of events after dose 2 at days 1-7, there were no important imbalances were noted for Vertigo, Vertigo Positional, Tinnitus, Fall and Road Traffic Accident

### 3.4 External Databases

No Disproportionate Reporting of Events Using EB05 > 2 (mRNA-1273 versus All vaccines in Adults) in VAERs as of 25 JUNE 2021.

### 3.5 Non-clinical Data

Not applicable

### 3.6 Epidemiological studies

Dizziness (defined based on the PTs of dizziness, dizziness exertional, dizziness postural, persistent postural-perceptual dizziness, procedural dizziness, vertigo, vertigo CNS origin, and vertigo positional) was observed in 20,080 cases cumulatively (reporting rate 191.14 per 100,000 person-years). This was below population-based estimates suggesting an annual incidence of approximately 3% per year (315,158 cases expected, rate ratio 0.06, 95% CI 0.06 – 0.06). Stratified analyses showed higher rates in women than men, however this was consistent with expectation. Sensitivity analyses assuming capture of 50% or 25% of cases in estimation of the reporting rate did not change the interpretation of findings

**Table-3: Observed/Expected Analyses Stratified by Age and Gender, Dizziness, Expected Rates from Germany**

|                   | Person-years | Observed |        | Expected |         | As observed: RR (95% CI) | Assuming 50% of cases were reported: RR (95% CI) | Assuming 25% of cases were reported: RR (95% CI) |
|-------------------|--------------|----------|--------|----------|---------|--------------------------|--------------------------------------------------|--------------------------------------------------|
|                   |              | Cases    | Rate   | Cases    | Rate    |                          |                                                  |                                                  |
| All               | 10,505,272   | 20,080   | 191.14 | 315158.2 | 3000.00 | 0.06 (0.06, 0.06)        | 0.13 (0.13, 0.13)                                | 0.25 (0.25, 0.26)                                |
| By age (years)    |              |          |        |          |         |                          |                                                  |                                                  |
| <18               |              |          |        |          |         | 0.01 (0.01, 0.01)        | 0.02 (0.01, 0.02)                                | 0.04 (0.03, 0.04)                                |
| 18-29             | 108,454      | 29       | 26.74  | 3226.5   | 2975.00 | 0.1 (0.09, 0.1)          | 0.2 (0.19, 0.2)                                  | 0.4 (0.39, 0.4)                                  |
| 30-39             | 865,795      | 2,547    | 294.18 | 25757.4  | 2975.00 | 0.07 (0.06, 0.07)        | 0.13 (0.13, 0.14)                                | 0.27 (0.26, 0.27)                                |
| 40-49             | 2,159,773    | 3,313    | 153.40 | 49890.8  | 2310.00 | 0.1 (0.1, 0.11)          | 0.21 (0.2, 0.21)                                 | 0.41 (0.4, 0.42)                                 |
| 50-64             | 1,527,656    | 3,152    | 206.33 | 30629.5  | 2005.00 | 0.09 (0.08, 0.09)        | 0.17 (0.17, 0.18)                                | 0.35 (0.34, 0.35)                                |
| 65-74             | 2,824,366    | 4,759    | 168.50 | 54792.7  | 1940.00 | 0.09 (0.09, 0.1)         | 0.18 (0.18, 0.19)                                | 0.37 (0.36, 0.38)                                |
| 75+               | 1,760,075    | 3,324    | 188.86 | 35993.5  | 2045.00 | 0.06 (0.06, 0.07)        | 0.13 (0.12, 0.13)                                | 0.25 (0.25, 0.26)                                |
| By gender         |              |          |        |          |         |                          |                                                  |                                                  |
| Male              |              |          |        |          |         |                          |                                                  |                                                  |
| Female            | 4,947,983    | 4,722    | 95.43  | 82631.3  | 1670.00 | 0.06 (0.06, 0.06)        | 0.11 (0.11, 0.12)                                | 0.23 (0.22, 0.23)                                |
|                   | 5,557,289    | 15,034   | 270.53 | 160605.7 | 2890.00 | 0.09 (0.09, 0.1)         | 0.19 (0.18, 0.19)                                | 0.37 (0.37, 0.38)                                |
| By age and gender |              |          |        |          |         |                          |                                                  |                                                  |
| Male              |              |          |        |          |         |                          |                                                  |                                                  |
| <18               |              |          |        |          |         | 0.01 (0, 0.01)           | 0.01 (0.01, 0.02)                                | 0.03 (0.02, 0.04)                                |
| 18-29             | 51,493       | 8        | 15.54  | 1081.4   | 2100.00 | 0.08 (0.07, 0.09)        | 0.16 (0.15, 0.17)                                | 0.32 (0.3, 0.33)                                 |
| 30-39             | 409,421      | 684      | 167.07 | 8597.8   | 2100.00 | 0.05 (0.05, 0.05)        | 0.1 (0.1, 0.11)                                  | 0.2 (0.2, 0.21)                                  |
| 40-49             | 1,021,322    | 832      | 81.46  | 16341.2  | 1600.00 | 0.05 (0.05, 0.06)        | 0.1 (0.1, 0.11)                                  | 0.21 (0.2, 0.22)                                 |
| 50-64             | 722,404      | 598      | 82.78  | 11486.2  | 1590.00 | 0.05 (0.05, 0.06)        | 0.11 (0.1, 0.11)                                 | 0.21 (0.21, 0.22)                                |
| 65-74             | 1,335,598    | 954      | 71.43  | 17763.5  | 1330.00 | 0.07 (0.07, 0.07)        | 0.14 (0.13, 0.15)                                | 0.28 (0.27, 0.29)                                |
| 75+               | 832,311      | 854      | 102.61 | 12235.0  | 1470.00 | 0.05 (0.05, 0.05)        | 0.1 (0.09, 0.11)                                 | 0.2 (0.19, 0.21)                                 |
| Female            |              |          |        |          |         |                          |                                                  |                                                  |
| <18               |              |          |        |          |         | 0.01 (0.01, 0.01)        | 0.02 (0.01, 0.02)                                | 0.04 (0.03, 0.04)                                |
| 18-29             | 57,834       | 20       | 34.58  | 2226.6   | 3850.00 | 0.1 (0.1, 0.11)          | 0.21 (0.2, 0.22)                                 | 0.42 (0.41, 0.43)                                |
| 30-39             | 459,837      | 1,855    | 403.40 | 17703.7  | 3850.00 | 0.07 (0.07, 0.07)        | 0.14 (0.14, 0.15)                                | 0.28 (0.28, 0.29)                                |
|                   | 1,147,090    | 2,463    | 214.72 | 34642.1  | 3020.00 |                          |                                                  |                                                  |

|                   | Person-years | Observed |        | Expected |         | As observed: RR (95% CI) | Assuming 50% of cases were reported: RR (95% CI) | Assuming 25% of cases were reported: RR (95% CI) |
|-------------------|--------------|----------|--------|----------|---------|--------------------------|--------------------------------------------------|--------------------------------------------------|
| 40-49             | 811,363      | 2,541    | 313.18 | 19635.0  | 2420.00 | 0.13 (0.12, 0.13)        | 0.26 (0.25, 0.27)                                | 0.52 (0.51, 0.53)                                |
| 50-64             | 1,500,066    | 3,782    | 252.12 | 38251.7  | 2550.00 | 0.1 (0.1, 0.1)           | 0.2 (0.19, 0.2)                                  | 0.4 (0.39, 0.4)                                  |
| 65-74             | 934,804      | 2,452    | 262.30 | 24491.9  | 2620.00 | 0.1 (0.1, 0.1)           | 0.2 (0.19, 0.21)                                 | 0.4 (0.39, 0.41)                                 |
| 75+               | 646,294      | 1,422    | 220.02 | 20875.3  | 3230.00 | 0.07 (0.06, 0.07)        | 0.14 (0.13, 0.14)                                | 0.27 (0.26, 0.28)                                |
|                   | Person-years | Observed |        | Expected |         | As observed: RR (95% CI) | Assuming 50% of cases were reported: RR (95% CI) | Assuming 25% of cases were reported: RR (95% CI) |
|                   |              | Cases    | Rate   | Cases    | Rate    |                          |                                                  |                                                  |
| All               | 10,505,272   | 209      | 1.99   | 1155.6   | 11.00   | 0.18 (0.16, 0.21)        | 0.36 (0.32, 0.4)                                 | 0.72 (0.66, 0.79)                                |
| By age (years)    |              |          |        |          |         |                          |                                                  |                                                  |
| <18               | 108,454      | 1        | 0.92   | 2.5      | 2.26    | 0.41 (0.04, 4.18)        | 0.82 (0.13, 5.28)                                | 1.63 (0.33, 8)                                   |
| 18-29             | 865,795      | 50       | 5.78   | 19.6     | 2.26    | 2.56 (1.52, 4.31)        | 5.11 (3.15, 8.3)                                 | 10.22 (6.43, 16.26)                              |
| 30-39             | 2,159,773    | 27       | 1.25   | 48.8     | 2.26    | 0.55 (0.35, 0.89)        | 1.11 (0.75, 1.63)                                | 2.21 (1.58, 3.1)                                 |
| 40-49             | 1,527,656    | 25       | 1.64   | 62.6     | 4.10    | 0.4 (0.25, 0.63)         | 0.8 (0.55, 1.16)                                 | 1.6 (1.16, 2.19)                                 |
| 50-64             | 2,824,366    | 31       | 1.10   | 587.5    | 20.80   | 0.05 (0.04, 0.08)        | 0.11 (0.08, 0.14)                                | 0.21 (0.17, 0.26)                                |
| 65-74             | 1,760,075    | 37       | 2.10   | 366.1    | 20.80   | 0.1 (0.07, 0.14)         | 0.2 (0.16, 0.26)                                 | 0.4 (0.33, 0.49)                                 |
| 75+               | 1,216,860    | 27       | 2.22   | 1332.3   | 109.49  | 0.02 (0.01, 0.03)        | 0.04 (0.03, 0.05)                                | 0.08 (0.07, 0.1)                                 |
| By gender         |              |          |        |          |         |                          |                                                  |                                                  |
| Male              | 4,947,983    | 65       | 1.31   | 354.3    | 7.16    | 0.18 (0.14, 0.24)        | 0.37 (0.3, 0.45)                                 | 0.73 (0.63, 0.86)                                |
| Female            | 5,557,289    | 138      | 2.48   | 823.6    | 14.82   | 0.17 (0.14, 0.2)         | 0.34 (0.29, 0.38)                                | 0.67 (0.6, 0.75)                                 |
| By age and gender |              |          |        |          |         |                          |                                                  |                                                  |
| Male              |              |          |        |          |         |                          |                                                  |                                                  |
| <18               | 51,493       | 0        | 0.00   | 1.2      | 2.41    | NA                       | NA                                               | NA                                               |
| 18-29             | 409,421      | 16       | 3.91   | 9.9      | 2.41    | 1.62 (0.73, 3.59)        | 3.24 (1.59, 6.62)                                | 6.49 (3.32, 12.68)                               |
| 30-39             | 1,021,322    | 2        | 0.20   | 24.6     | 2.41    | 0.08 (0.02, 0.34)        | 0.16 (0.06, 0.47)                                | 0.33 (0.15, 0.72)                                |
| 40-49             | 722,404      | 10       | 1.38   | 27.6     | 3.82    | 0.36 (0.18, 0.75)        | 0.72 (0.41, 1.29)                                | 1.45 (0.89, 2.35)                                |
| 50-64             | 1,335,598    | 11       | 0.82   | 204.7    | 15.33   | 0.05 (0.03, 0.1)         | 0.11 (0.07, 0.17)                                | 0.21 (0.16, 0.3)                                 |
| 65-74             | 832,311      | 15       | 1.80   | 127.6    | 15.33   | 0.12 (0.07, 0.2)         | 0.24 (0.16, 0.35)                                | 0.47 (0.35, 0.64)                                |
| 75+               | 575,434      | 9        | 1.56   | 767.3    | 133.35  | 0.01 (0.01, 0.02)        | 0.02 (0.01, 0.04)                                | 0.05 (0.03, 0.07)                                |
| Female            |              |          |        |          |         |                          |                                                  |                                                  |
| <18               | 57,834       | 1        | 1.73   | 1.2      | 2.10    | 0.82 (0.06, 11.61)       | 1.65 (0.17, 15.7)                                | 3.29 (0.43, 25.09)                               |
| 18-29             | 459,837      | 34       | 7.39   | 9.7      | 2.10    | 3.52 (1.72, 7.2)         | 7.04 (3.59, 13.82)                               | 14.08 (7.33, 27.05)                              |
| 30-39             | 1,147,090    | 25       | 2.18   | 24.1     | 2.10    | 1.04 (0.59, 1.82)        | 2.08 (1.28, 3.37)                                | 4.15 (2.66, 6.48)                                |
| 40-49             | 811,363      | 15       | 1.85   | 35.5     | 4.37    | 0.42 (0.23, 0.77)        | 0.85 (0.52, 1.38)                                | 1.69 (1.12, 2.56)                                |
| 50-64             | 1,500,066    | 20       | 1.33   | 381.9    | 25.46   | 0.05 (0.03, 0.08)        | 0.1 (0.08, 0.15)                                 | 0.21 (0.16, 0.27)                                |

|       | Person-years | Observed | Expected     | As observed: RR (95% CI) | Assuming 50% of cases were reported: RR (95% CI) | Assuming 25% of cases were reported: RR (95% CI) |
|-------|--------------|----------|--------------|--------------------------|--------------------------------------------------|--------------------------------------------------|
| 65-74 | 934,804      | 22 2.35  | 238.0 25.46  | 0.09 (0.06, 0.14)        | 0.18 (0.13, 0.26)                                | 0.37 (0.29, 0.47)                                |
| 75+   | 646,294      | 18 2.79  | 861.8 133.35 | 0.02 (0.01, 0.03)        | 0.04 (0.03, 0.06)                                | 0.08 (0.07, 0.11)                                |

\*Rates per 100,000 person-years. Neuhauser HK. The epidemiology of dizziness and vertigo. Handb Clin Neurol. 2016;137:67-82. doi: 10.1016/B978-0-444-63437-5.00005-4. PMID: 27638063.

The source material described annual incidence, but age and sex stratification were provided based on prevalence. Estimates used to calculate expected cases assume that 10% of prevalent cases were incident.

### 3.6.1 Tinnitus

Tinnitus (defined based on the PT of tinnitus alone) was observed in 2,316 cases cumulatively (reporting rate 22.05 per 100,000 person-years). This was below population-based estimates suggesting an incidence of approximately 54 per 100,000 person-years (5,672.8 cases expected, rate ratio 0.41, 95% CI 0.39 – 0.43). Stratified analyses showed higher rates in men and older individuals; however, this was consistent with expectation. Sensitivity analyses assuming capture of 50% cases in estimation of the reporting rate suggest a potential increase in the rate of tinnitus for younger women (Table-4).

**Table 4: Observed/Expected Analyses Stratified by Age and Gender, Tinnitus, Expected Rates from England**

|                   | Person-years | Observed |       | Expected |        | As observed: RR (95% CI) | Assuming 50% of cases were reported: RR (95% CI) | Assuming 25% of cases were reported: RR (95% CI) |
|-------------------|--------------|----------|-------|----------|--------|--------------------------|--------------------------------------------------|--------------------------------------------------|
|                   |              | Cases    | Rate  | Cases    | Rate   |                          |                                                  |                                                  |
| All               | 10,505,272   | 2,316    | 22.05 | 5672.8   | 54.00  | 0.41 (0.39, 0.43)        | 0.82 (0.79, 0.85)                                | 1.63 (1.58, 1.69)                                |
| By age (years)    |              |          |       |          |        |                          |                                                  |                                                  |
| <18               | 108,454      | 2        | 1.84  | 2.2      | 2.00   | 0.92 (0.13, 6.30)        | 1.84 (0.35, 9.63)                                | 3.69 (0.82, 16.54)                               |
| 18-29             | 865,795      | 126      | 14.55 | 190.5    | 22.00  | 0.66 (0.53, 0.83)        | 1.32 (1.1, 1.6)                                  | 2.65 (2.24, 3.13)                                |
| 30-39             | 2,159,773    | 276      | 12.78 | 842.3    | 39.00  | 0.33 (0.29, 0.38)        | 0.66 (0.59, 0.73)                                | 1.31 (1.20, 1.43)                                |
| 40-49             | 1,527,656    | 387      | 25.33 | 947.1    | 62.00  | 0.41 (0.36, 0.46)        | 0.82 (0.74, 0.9)                                 | 1.63 (1.51, 1.77)                                |
| 50-64             | 2,824,366    | 812      | 28.75 | 2909.1   | 103.00 | 0.28 (0.26, 0.30)        | 0.56 (0.53, 0.59)                                | 1.12 (1.06, 1.17)                                |
| 65-74             | 1,760,075    | 461      | 26.19 | 1601.7   | 91.00  | 0.29 (0.26, 0.32)        | 0.58 (0.53, 0.62)                                | 1.15 (1.08, 1.23)                                |
| 75+               | 1,216,860    | 110      | 9.04  | 778.8    | 64.00  | 0.14 (0.12, 0.17)        | 0.28 (0.24, 0.33)                                | 0.56 (0.50, 0.64)                                |
| By gender         |              |          |       |          |        |                          |                                                  |                                                  |
| Male              | 4,947,983    | 845      | 17.08 | 2721.4   | 55.00  | 0.31 (0.29, 0.34)        | 0.62 (0.58, 0.66)                                | 1.24 (1.18, 1.31)                                |
| Female            | 5,557,289    | 1,425    | 25.64 | 2945.4   | 53.00  | 0.48 (0.45, 0.52)        | 0.97 (0.92, 1.02)                                | 1.94 (1.85, 2.02)                                |
| By age and gender |              |          |       |          |        |                          |                                                  |                                                  |
| Male              |              |          |       |          |        |                          |                                                  |                                                  |
| <18               | 51,493       | 1        | 1.94  | 1.0      | 2.00   | 0.97 (0.06, 15.21)       | 1.94 (0.18, 20.92)                               | 3.88 (0.45, 33.87)                               |
| 18-29             | 409,421      | 38       | 9.28  | 94.2     | 23.00  | 0.40 (0.28, 0.59)        | 0.81 (0.6, 1.09)                                 | 1.61 (1.25, 2.09)                                |

|        |           |     |       |        |        |                    |                    |                    |
|--------|-----------|-----|-------|--------|--------|--------------------|--------------------|--------------------|
| 30-39  | 1,021,322 | 108 | 10.57 | 388.1  | 38.00  | 0.28 (0.22, 0.34)  | 0.56 (0.47, 0.66)  | 1.11 (0.97, 1.28)  |
| 40-49  | 722,404   | 159 | 22.01 | 476.8  | 66.00  | 0.33 (0.28, 0.40)  | 0.67 (0.58, 0.77)  | 1.33 (1.18, 1.50)  |
| 50-64  | 1,335,598 | 304 | 22.76 | 1415.7 | 106.00 | 0.21 (0.19, 0.24)  | 0.43 (0.39, 0.47)  | 0.86 (0.80, 0.93)  |
| 65-74  | 832,311   | 156 | 18.74 | 715.8  | 86.00  | 0.22 (0.18, 0.26)  | 0.44 (0.38, 0.5)   | 0.87 (0.78, 0.97)  |
| 75+    | 575,434   | 41  | 7.13  | 345.3  | 60.00  | 0.12 (0.09, 0.16)  | 0.24 (0.19, 0.3)   | 0.48 (0.39, 0.57)  |
| Female |           |     |       |        |        |                    |                    |                    |
| <18    |           |     |       |        |        | 0.86 (0.06, 12.56) | 1.73 (0.18, 17.07) | 3.46 (0.44, 27.38) |
|        | 57,834    | 1   | 1.73  | 1.2    | 2.00   |                    |                    |                    |
| 18-29  | 459,837   | 88  | 19.14 | 92.0   | 20.00  | 0.96 (0.71, 1.28)  | 1.91 (1.49, 2.46)  | 3.83 (3.04, 4.81)  |
| 30-39  | 1,147,090 | 168 | 14.65 | 447.4  | 39.00  | 0.38 (0.31, 0.45)  | 0.75 (0.65, 0.87)  | 1.50 (1.33, 1.69)  |
| 40-49  | 811,363   | 226 | 27.85 | 478.7  | 59.00  | 0.47 (0.4, 0.55)   | 0.94 (0.83, 1.07)  | 1.89 (1.69, 2.11)  |
| 50-64  | 1,500,066 | 501 | 33.40 | 1500.1 | 100.00 | 0.33 (0.30, 0.37)  | 0.67 (0.62, 0.72)  | 1.34 (1.25, 1.43)  |
| 65-74  | 934,804   | 305 | 32.63 | 888.1  | 95.00  | 0.34 (0.30, 0.39)  | 0.69 (0.62, 0.76)  | 1.37 (1.26, 1.50)  |
| 75+    | 646,294   | 69  | 10.68 | 433.0  | 67.00  | 0.16 (0.12, 0.21)  | 0.32 (0.26, 0.39)  | 0.64 (0.55, 0.74)  |

\*Rates per 100,000 person-years. Martinez C, Wallenhorst C, McFerran D, Hall DA. Incidence rates of clinically significant tinnitus: 10-year trend from a cohort study in England. *Ear Hear.* 2015;36(3):e69-e75. doi:10.1097/AUD.0000000000000121

### 3.7 Review of the Pharmacovigilance Database

Post marketing data for validated signal of Dizziness was cumulatively reviewed in the MAH Global safety database with a data-lock point (DLP) of 30 June 2020. The term Dizziness was analysed by using a cluster of MedDRA PTs dizziness, dizziness exertional, dizziness postural, persistent postural-perceptual dizziness, procedural dizziness, vertigo, vertigo CNS origin, vertigo positional, cumulatively, there were 20,080 cases (21,265 events) that involved 4,185 serious cases (1,429 events). There were 24 cases with fatal outcome. A breakdown of the cases reported by gender was 4,722 males, 15,034 females, and 81 unknown, with a mean age of 51.3 years (SD: 17.9) and a median age of 51 years.

### 3.8 Results

This review has been segmented to focus on Dizziness in conjunction with HLT Inner Ear (which includes the PT tinnitus), HLT Non-Site Injuries, or vaccine reactogenicity.

**Table-4: Serious events by Preferred Terms in the HLT Inner Ear**

| Preferred Term            | Serious  |                   |
|---------------------------|----------|-------------------|
|                           | # Events | % of Total Events |
| Vertigo                   | 213      | 68.7%             |
| Tinnitus                  | 61       | 19.7%             |
| Vertigo positional        | 9        | 2.9%              |
| Motion sickness           | 4        | 1.3%              |
| Vestibular disorder       | 9        | 2.9%              |
| Meniere's disease         | 11       | 3.5%              |
| Inner ear disorder        | 1        | 0.3%              |
| Acute vestibular syndrome | 1        | 0.3%              |
| Inner ear inflammation    | 1        | 0.3%              |



|              |     |        |
|--------------|-----|--------|
| Otolithiasis | -   | -      |
| Grand total  | 310 | 100.0% |

Of the 2,404 cases related to the HLT inner ear, 1,658 (69.0%) were medically confirmed. Gender distribution was 617 male and 1,740 female with 13 missing. Mean age was 54.2 years (SD:16.1) and median age was 55; there were 121 cases with missing age.

The most commonly reported time to onset of events was less than 7 days from administration of mRNA-1273 (71.7%) ([Table-5](#))

**Table 5: Distribution of Cumulative Events by First Dose Latency for the Dizziness Events with HLT Inner Ear**

|                             | Events | %    |
|-----------------------------|--------|------|
| <b>Latency Since Dose 1</b> |        |      |
| < 7 days                    | 1741   | 71.7 |
| 7 to < 14 days              | 242    | 10.0 |
| 14 to < 30 days             | 180    | 7.4  |
| ≥ 30 days                   | 129    | 5.3  |
| Missing                     | 315    | 13.0 |

Last dose latency average in days was 4.6 (SD8.5). Median in days was 2, with range 0 to 55. There were 2371 missing values.

Seven hundred and twelve of the events were reported as resolved, 135 events were resolving, 9 events resolved with sequelae, 1,015 events had not resolved, and 723 were missing/unknown/other. Zero fatal outcomes were reported. [Table-6](#) below presents outcome stratified by age group and latency. Note that there is a potential for interpretation bias for cases reported as (not recovered/not resolved) as this categorization was made at the time of report and may not capture information following that point of time. The majority of cases were obtained from VAERS, without available follow up information.

**Table 6: Event Outcome by Age and Latency**

| First Dose Latency Group Ordered | Event Outcome | 0-17 | 18-29 | 30-39 | 40-49 | 51-64 | 65-74 | 75-84 | 85+ | Missing | Grand total |
|----------------------------------|---------------|------|-------|-------|-------|-------|-------|-------|-----|---------|-------------|
| <7 days                          | Subtotal      | 1    | 144   | 245   | 292   | 558   | 330   | 125   | 15  | 31      | 1,741       |

|                  |                                         |   |    |     |     |     |     |    |   |    |     |
|------------------|-----------------------------------------|---|----|-----|-----|-----|-----|----|---|----|-----|
|                  | Not Recovered/<br>Not Resolved          | - | 49 | 108 | 134 | 258 | 119 | 49 | 4 | 6  | 727 |
|                  | Recovered/<br>Resolved                  | - | 59 | 80  | 89  | 150 | 120 | 43 | 6 | 6  | 553 |
|                  | Recovered/<br>Resolved with<br>Sequelae | - | 2  | -   | 1   | 4   | -   | -  | - | 2  | 9   |
|                  | Recovering/<br>Resolving                | - | 9  | 16  | 23  | 25  | 8   | 7  | 1 | 2  | 91  |
|                  | Unknown                                 | 1 | 23 | 41  | 45  | 119 | 83  | 26 | 4 | 14 | 356 |
|                  | (Empty)                                 | - | 2  | -   | -   | 2   | -   | -  | - | 1  | 5   |
| ≥7d and<br><14d  | Subtotal                                |   | 6  | 29  | 43  | 80  | 50  | 27 | 4 | 3  | 242 |
|                  | Not Recovered/<br>Not Resolved          | - | 3  | 21  | 23  | 45  | 20  | 7  | 1 | 1  | 121 |
|                  | Recovered/<br>Resolved                  | - | 1  | 4   | 9   | 7   | 17  | 7  | - | 2  | 47  |
|                  | Recovering/<br>Resolving                | - | -  | 2   | 5   | 6   | 1   | 1  | - | -  | 15  |
|                  | Unknown                                 | - | 2  | 2   | 6   | 22  | 12  | 12 | 3 | -  | 59  |
| ≥14d and<br><30d | Subtotal                                |   | 7  | 26  | 21  | 49  | 50  | 23 | 1 | 3  | 180 |
|                  | Not Recovered/<br>Not Resolved          | - | 3  | 13  | 14  | 16  | 23  | 6  | 1 | -  | 76  |
|                  | Recovered/<br>Resolved                  | - | 1  | 5   | 3   | 9   | 9   | 7  | - | 2  | 36  |
|                  | Recovering/<br>Resolving                | - | -  | 3   | -   | 2   | -   | -  | - | -  | 5   |
|                  | Unknown                                 | - | 3  | 5   | 4   | 22  | 18  | 10 | - | 1  | 63  |
| ≥30d             | Subtotal                                |   | 6  | 15  | 19  | 44  | 22  | 15 | 2 | 6  | 129 |
|                  | Not Recovered/<br>Not Resolved          | - | 1  | 6   | 7   | 20  | 2   | 2  | 1 | 1  | 40  |

|         |                                   |   |    |    |    |    |    |    |   |    |     |
|---------|-----------------------------------|---|----|----|----|----|----|----|---|----|-----|
|         | Recovered/<br>Resolved            | - | 2  | 6  | 6  | 8  | 7  | 4  | - | 3  | 36  |
|         | Recovering/<br>Resolving          | - | 1  | 3  | -  | 2  | 1  | -  | - | -  | 7   |
|         | Unknown                           | - | 2  | -  | 6  | 14 | 12 | 9  | 1 | 2  | 46  |
| Missing | Subtotal                          | 3 | 14 | 24 | 34 | 61 | 54 | 30 | 6 | 89 | 315 |
|         | Not<br>Recovered/<br>Not Resolved | 3 | 5  | 4  | 4  | 12 | 11 | 4  | 2 | 6  | 51  |
|         | Recovered/<br>Resolved            | - | 2  | 1  | 6  | 8  | 10 | 9  | - | 4  | 40  |
|         | Recovering/<br>Resolving          | - | 2  | 2  | 7  | 3  | 1  | -  | - | 2  | 17  |
|         | Unknown                           | - | 4  | 16 | 17 | 38 | 27 | 17 | 4 | 76 | 199 |
|         | (Empty)                           | - | 1  | 1  | -  | -  | 5  | -  | - | 1  | 8   |

The 3 serious cases with a duration of 7 days or more in association with mRNA-1273 are described in [Table-7](#).

**Table 7: Serious Cases of Dizziness with HLT Inner Ear Without Confounders**

| Case ID#          | Age /<br>Sex | PT                             | TTO / Duration | Outcome  |
|-------------------|--------------|--------------------------------|----------------|----------|
| 4.1(b) [REDACTED] | 41/F         | Loss of consciousness, Vertigo | 1/8            | resolved |
| 4.1(b) [REDACTED] | 53/M         | Vertigo                        | 17/18          | resolved |
| 4.1(b) [REDACTED] | 55/M         | Tinnitus                       | 1/11           | resolved |

Based on this cumulative review, there is insufficient evidence at this time of a causal association between mRNA-1273 and prolonged duration (7+ days) of dizziness with HLT Inner Ear.

There were 2 reports of fatal cases, a 54-year-old female patient (Case# 4.1(b) [REDACTED]). History of alcohol abuse, hepatic cirrhosis & steatohepatitis, ascites, nicotine abuse, depression, hypertension, hypertensive gastropathy, gastric banding, hypoalbuminemia, splenomegaly. Experienced vertigo the day of administration of first dose of mRNA-1273. 30 days later the patient experienced vertigo along with cardiovascular collapse and died. MAH Summary: this



patient had severe multisystem chronic disease related to alcohol abuse. She experienced vertigo on the day of vaccination; her death with cardiovascular collapse occurred 30 days later, also with vertigo at that time. No clear evidence the vaccine played a role.

Another report of fatal case was in 72-year-old male patient (4.1(b)). History of coronary artery bypass graft, Type 2 diabetes mellitus, Heart failure with 35% ejection fraction, Atrial fibrillation, Coronary artery disease, Hypothyroidism, Anxiety, Hypertension, Gout and GERD. Received mRNA-1273 on 17-Jan-2021. The patient received first dose of mRNA-1273 (Moderna COVID-19 Vaccine) (Intramuscular) 1 dosage form. On 21-Feb-2021, the patient experienced Guillain-Barre syndrome (35-day interval post-vaccination), including hypotension, dizziness, a fall, muscle atrophy and gait disturbance and tremor. The patient died on 23-Apr-2021. The reported cause of death was Guillain-Barre syndrome (GBS). MAH Summary: Dizziness in this patient was not a primary medical issue; the primary medical issue was GBS with a 35-day interval post-vaccination. This 35-day interval is longer than the typical interval for vaccine-associated GBS. Indeed CDC's Vaccine Safety Datalink Rapid Cycle Analysis screening for a potential link between GBS and vaccination against SARS Covid-2 disease uses only a 21-day interval.

Serious events by Preferred Terms in the HLT Non-Site Injuries by frequency is presented in [Table-8](#).

**Table-8: Serious Events by Preferred Terms in the HLT Non-Site Injuries**

| Preferred Term              | Serious  |                   |
|-----------------------------|----------|-------------------|
|                             | # Events | % of Total Events |
| Fall                        | 69       | 94.5              |
| Road traffic accident       | 2        | 2.7               |
| Child Maltreatment syndrome | 2        | 2.7               |
| Grand total                 | 73       | 100.0%            |

**Table-9: Distribution of Cumulative Events by First Dose Latency for the Dizziness Events with HLT Non-Site Injuries**

|                             | Events | %    |
|-----------------------------|--------|------|
| <b>Latency Since Dose 1</b> |        |      |
| < 7 days                    | 427    | 83.2 |
| 7 to < 14 days              | 18     | 3.5  |
| 14 to < 30 days             | 16     | 3.1  |
| ≥ 30 days                   | 19     | 3.7  |
| Missing                     | 33     | 6.4  |

Last dose latency in days was an average of 2.6 (SD 3.7); the median in days was 2 (min 0, max 14)

The following [Table-10](#) below presents outcome for Dizziness with HLT Non-Site Injuries stratified by age group and latency. Note that there is a potential for interpretation bias for cases reported as (not recovered/not resolved) as this categorization was made at the time of report and may not capture information following that point of time. The majority of cases were obtained from VAERS, without available follow up information.

**Table 10: Outcome for Dizziness with HLT Non-Site Injuries Stratified by Age Group and Latency**

| First Dose Latency Group Ordered | Event Outcome                     | 0-17 | 18-29 | 30-39 | 40-49 | 51-64 | 65-74 | 75-84 | 85+ | Missing | Grand total |
|----------------------------------|-----------------------------------|------|-------|-------|-------|-------|-------|-------|-----|---------|-------------|
| <7 days                          | Subtotal                          | 1    | 92    | 71    | 46    | 61    | 76    | 57    | 15  | 8       | 427         |
|                                  | Not Recovered/ Not Resolved       | -    | 5     | 9     | 9     | 15    | 19    | 17    | 3   | -       | 77          |
|                                  | Recovered/ Resolved               | -    | 56    | 42    | 23    | 32    | 28    | 20    | 7   | 4       | 212         |
|                                  | Recovered/ Resolved with Sequelae | -    | -     | -     | -     | 1     | -     | -     | -   | -       | 1           |
|                                  | Recovering/ Resolving             | -    | -     | -     | -     | 1     | 1     | 1     | -   | -       | 3           |
|                                  | Unknown                           | 1    | 31    | 20    | 14    | 12    | 28    | 18    | 5   | 4       | 133         |
|                                  | (Empty)                           | -    | -     | -     | -     | -     | -     | 1     | -   | -       | 1           |
| >=7d and <14d                    | Subtotal                          |      |       |       | 2     | 2     | 5     | 4     | 5   |         | 18          |
|                                  | Not Recovered/ Not Resolved       | -    | -     | -     | 1     | 1     | 2     | 1     | 2   | -       | 7           |
|                                  | Recovered/ Resolved               | -    | -     | -     | -     | -     | 3     | 2     | -   | -       | 5           |
|                                  | Unknown                           | -    | -     | -     | 1     | 1     | -     | 1     | 3   | -       | 6           |
| >=14d and <30d                   | Subtotal                          |      | 2     | 1     | 1     | 5     | 2     | 3     | 1   | 1       | 16          |
|                                  | Not Recovered/ Not Resolved       | -    | -     | -     | 1     | 2     | -     | -     | 1   | 1       | 5           |
|                                  | Recovered/ Resolved               | -    | 1     | -     | -     | 1     | 1     | -     | -   | -       | 3           |
|                                  | Recovering/ Resolving             | -    | -     | -     | -     | 2     | -     | -     | -   | -       | 2           |
|                                  | Unknown                           | -    | 1     | 1     | -     | -     | 1     | 3     | -   | -       | 6           |

|         |                                |   |   |   |   |   |   |   |   |   |    |
|---------|--------------------------------|---|---|---|---|---|---|---|---|---|----|
| ≥30d    | Subtotal                       |   | 1 | 1 | 2 | 4 | 6 | 5 |   |   | 19 |
|         | Fatal                          | - | - | - | - | 1 | 1 | - | - | - | 2  |
|         | Recovered/<br>Resolved         | - | 1 | - | - | 2 | 2 | 2 | - | - | 7  |
|         | Recovering/<br>Resolving       | - | - | 1 | - | - | - | - | - | - | 1  |
|         | Unknown                        | - | - | - | 2 | 1 | 3 | 3 | - | - | 9  |
| Missing | Subtotal                       |   | 2 | 1 | 1 | 6 | 7 | 9 | 4 | 3 | 33 |
|         | Not Recovered/ Not<br>Resolved | - | - | - | - | 3 | - | 1 | 1 | - | 5  |
|         | Recovered/<br>Resolved         | - | - | - | - | 1 | 1 | 1 | - | - | 3  |
|         | Recovering/<br>Resolving       | - | 1 | - | - | - | - | - | - | - | 1  |
|         | Unknown                        | - | 1 | 1 | 1 | 2 | 5 | 7 | 3 | 3 | 23 |
|         | (Empty)                        | - | - | - | - | - | 1 | - | - | - | 1  |

Of all the dizziness events with HLT Non-site injuries, no events had a duration of 7 days or greater.

**Table-11: Duration of Events, Dizziness with HLT Non-Site Injury**

| Duration   | Events | %    |
|------------|--------|------|
| ≤ 1 day    | 32     | 6.2  |
| 2-3 days   | 2      | 0.4  |
| 4-7 days   | 1      | 0.2  |
| >7-29 days | 0      | 0    |
| ≥ 30 days  | 0      | 0    |
| Empty      | 478    | 93.2 |
| Total      | 513    | 100  |

Review of Dizziness with Road Traffic Accident: A 54-year-old female patient (Case ID: 4.1(b) [REDACTED]) with hypertension and medications AMLODIPINE, ATORVASTATIN, VITAMIN D and LINACLOTIDE for an unknown indication. On day of first dose mRNA-1273 the patient experienced a road traffic accident. MAH Summary: It was not reported whether the patient was driving or whether the symptoms of dizziness, headache or feeling abnormal occurred prior or

subsequent to the accident. The patient suffered a fractured wrist. At the time of report the adverse events had resolved.

A 74-year-old female patient (case ID: 4.1(b) ). Concomitant products included Amlodipine, Lovastatin, Calcium, Folic Acid and Gabapentin. 23 days following second dose of vaccine, the patient experienced dizziness and a road traffic accident. It was not reported whether the patient was driving or whether the symptoms of dizziness, headache or feeling abnormal occurred prior or subsequent to the accident. At the time of report the adverse events had resolved.

No serious reports that included dizziness mentioned injury due to the operation of machinery.

For the PTs dizziness, dizziness exertional, dizziness postural, persistent postural-perceptual dizziness, procedural dizziness, vertigo, vertigo CNS origin, vertigo positional, , cumulatively, in association with PTs that are involved in Reactogenicity, there were 13,637 cases (39,700 events) that involved 2,691 serious cases (2,074 serious events). There were 15 cases with fatal outcome. A breakdown of the cases reported by gender was 2,744 males and 10,079 females and 48 unknown, with a mean age of 51.2 years (SD: 16.8) and a median age of 51 years [min: 0 / max 121]). For the reporting period, there were 2894 cases (8,237 events) that involved 1106 serious cases.

The Table-12, below presents serious event PTs associated with Reactogenicity that occurred in conjunction with Dizziness. As expected, the median time to onset was one day.

**Table-12: Serious Event PTs associated with Reactogenicity in reports with Dizziness**

| Preferred Terms     | Serious  |                   |
|---------------------|----------|-------------------|
|                     | # Events | % of Total Events |
| Headache            | 332      | 16.0              |
| Nausea              | 366      | 17.6              |
| Fatigue             | 247      | 11.9              |
| Chills              | 163      | 7.9               |
| Pyrexia             | 211      | 10.2              |
| Pain                | 97       | 4.7               |
| Myalgia             | 118      | 5.7               |
| Vomiting            | 187      | 9.0               |
| Arthralgia          | 73       | 3.5               |
| Injection site pain | 29       | 1.4               |
| Malaise             | 104      | 5.0               |

The following table presents outcome for Dizziness in persons with PTs associated with reactogenicity stratified by age group and latency. Note that there is a potential for interpretation

bias for cases reported as (not recovered/not resolved) as this categorization was made at the time of report and may not capture information following that point of time. The majority of cases were obtained from VAERS, without available follow up information.

**Table-13: Event of Reactogenicity in reports with Dizziness Stratified by Age Group and Latency**

| First Dose Latency Group Ordered | All Event Outcome                       | 0-17 | 18-29 | 30-39 | 40-49 | 51-64 | 65-74 | 75-84 | 85+ | Missing | Grand total |
|----------------------------------|-----------------------------------------|------|-------|-------|-------|-------|-------|-------|-----|---------|-------------|
| <7 days                          | Subtotal                                | 18   | 3,821 | 5,580 | 5,430 | 8,545 | 5,215 | 1,906 | 337 | 683     | 31,535      |
|                                  | Fatal                                   | -    | -     | 1     | -     | -     | 3     | 7     | 1   | -       | 12          |
|                                  | Not Recovered/<br>Not Resolved          | 1    | 1,192 | 1,952 | 1,837 | 2,507 | 1,387 | 522   | 65  | 86      | 9,549       |
|                                  | Recovered/<br>Resolved                  | 12   | 1,695 | 2,381 | 2,261 | 3,719 | 2,350 | 776   | 133 | 241     | 13,568      |
|                                  | Recovered/<br>Resolved with<br>Sequelae | -    | 7     | 2     | 4     | 12    | -     | 1     | 1   | 1       | 28          |
|                                  | Recovering/<br>Resolving                | 1    | 157   | 190   | 178   | 305   | 88    | 56    | 11  | 45      | 1,031       |
|                                  | Unknown                                 | 4    | 762   | 1,034 | 1,146 | 1,985 | 1,380 | 539   | 126 | 307     | 7,283       |
|                                  | (Empty)                                 | -    | 8     | 20    | 4     | 17    | 7     | 5     | -   | 3       | 64          |
| >=7d and <14d                    | Subtotal                                |      | 121   | 298   | 409   | 485   | 331   | 185   | 24  | 34      | 1,887       |
|                                  | Fatal                                   | -    | -     | 3     | -     | 3     | -     | -     | -   | -       | 6           |
|                                  | Not Recovered/<br>Not Resolved          | -    | 50    | 145   | 199   | 166   | 76    | 41    | 11  | 2       | 690         |
|                                  | Recovered/<br>Resolved                  | -    | 18    | 87    | 88    | 127   | 97    | 68    | 4   | 8       | 497         |
|                                  | Recovering/<br>Resolving                | -    | 1     | 16    | 27    | 27    | 12    | 4     | -   | -       | 87          |
|                                  | Unknown                                 | -    | 50    | 47    | 95    | 162   | 146   | 72    | 9   | 24      | 605         |
|                                  | (Empty)                                 | -    | 2     | -     | -     | -     | -     | -     | -   | -       | 2           |
|                                  |                                         |      |       |       |       |       |       |       |     |         |             |
| >=14d and <30d                   | Subtotal                                |      | 82    | 171   | 199   | 416   | 287   | 166   | 18  | 25      | 1,364       |
|                                  | Fatal                                   | -    | -     | -     | -     | -     | 3     | 1     | -   | -       | 4           |
|                                  | Not Recovered/<br>Not Resolved          | -    | 19    | 29    | 44    | 105   | 62    | 23    | 1   | 6       | 289         |
|                                  | Recovered/<br>Resolved                  | -    | 32    | 70    | 83    | 131   | 86    | 61    | 4   | 6       | 473         |
|                                  | Recovered/<br>Resolved with<br>Sequelae | -    | -     | -     | 5     | -     | 1     | -     | -   | -       | 6           |
|                                  | Recovering/<br>Resolving                | -    | 16    | 20    | 26    | 18    | 7     | 8     | -   | -       | 95          |
|                                  | Unknown                                 | -    | 15    | 51    | 41    | 159   | 126   | 72    | 13  | 13      | 490         |
|                                  | (Empty)                                 | -    | -     | 1     | -     | 3     | 2     | 1     | -   | -       | 7           |
| >=30d                            | Subtotal                                |      | 71    | 160   | 197   | 458   | 293   | 147   | 22  | 37      | 1,385       |
|                                  | Fatal                                   | -    | -     | -     | -     | -     | -     | 2     | -   | -       | 2           |
|                                  | Not Recovered/<br>Not Resolved          | -    | 7     | 29    | 22    | 93    | 41    | 13    | 2   | 8       | 215         |

|         |                                        |    |     |     |     |     |     |     |    |     |       |
|---------|----------------------------------------|----|-----|-----|-----|-----|-----|-----|----|-----|-------|
|         | Recovered/<br>Resolved                 | -  | 45  | 75  | 97  | 155 | 73  | 35  | 12 | 10  | 502   |
|         | Recovered/<br>Resolved with<br>Sequela | -  | -   | -   | -   | 7   | -   | 2   | -  | -   | 9     |
|         | Recovering/<br>Resolving               | -  | 6   | 13  | 27  | 49  | 8   | 10  | 1  | -   | 114   |
|         | Unknown                                | -  | 12  | 43  | 47  | 149 | 158 | 85  | 7  | 18  | 519   |
|         | (Empty)                                | -  | 1   | -   | 4   | 5   | 13  | -   | -  | 1   | 24    |
| Missing | Subtotal                               | 11 | 267 | 390 | 436 | 802 | 622 | 273 | 67 | 661 | 3,529 |
|         | Not Recovered/<br>Not Resolved         | 3  | 56  | 37  | 49  | 84  | 48  | 24  | 8  | 74  | 383   |
|         | Recovered/<br>Resolved                 | 3  | 45  | 109 | 103 | 144 | 83  | 37  | 9  | 95  | 628   |
|         | Recovered/<br>Resolved with<br>Sequela | -  | -   | 5   | -   | 5   | 6   | -   | -  | 1   | 17    |
|         | Recovering/<br>Resolving               | 4  | 42  | 61  | 77  | 51  | 11  | 10  | 1  | 47  | 304   |
|         | Unknown                                | 1  | 120 | 163 | 199 | 488 | 462 | 201 | 49 | 425 | 2,108 |
|         | (Empty)                                | -  | 4   | 15  | 8   | 30  | 12  | 1   | -  | 19  | 89    |

**Table 14: Fatal Cases in persons with dizziness and also PTs associated with reactogenicity**

| Case ID | Age/Sex | PTs / Info                                                                                                                                                                                                     | TTO/Duration |
|---------|---------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|
| 4.1(b)  | 75/M    | Death, Dizziness, Malaise/<br>Died in sleep. Limited info                                                                                                                                                      | 2/0          |
| 4.1(b)  | 84/F    | Cyanosis, Diarrhoea haemorrhagic,<br>Dizziness, Nausea, Toothache,<br>Unresponsive to stimuli                                                                                                                  | 0/0          |
| 4.1(b)  | 83/F    | Blister, Chills, Dizziness, Fatigue/<br>Autopsy pending                                                                                                                                                        | 1/0          |
| 4.1(b)  | 70/M    | Cold sweat, Death, Dizziness, Fatigue,<br>Headache, Hyperhidrosis, Myocardial<br>infarction, Pain, Pain in extremity /<br>Myocardial infarction 20 days after<br>first dose. Died 40 days after first<br>dose. | 20/20        |
| 4.1(b)  | 79/M    | Asthenia, Chills, Diarrhoea,<br>Dizziness, Dyspnoea, Hyperhidrosis /<br>multiple serious chronic diseases.<br>Cause of death not reported.                                                                     | 3/NA         |
| 4.1(b)  | 78/F    | Aphasia, Decreased appetite,<br>Dizziness, Dyspnoea, Fatigue,                                                                                                                                                  | 0/8          |

|        |      |                                                                                                                                                                                                                                                                                                                           |      |
|--------|------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|
|        |      | Immediate post-injection reaction, Nausea, Respiratory failure / multiple serious chronic diseases                                                                                                                                                                                                                        |      |
| 4.1(b) | 73/F | Acute kidney injury, Confusional state, Death, Decreased appetite, Dizziness, Lethargy, Malaise, Nausea, Retinal vascular thrombosis, Somnolence                                                                                                                                                                          | 0/7  |
| 4.1(b) | 35/M | / Dizzy one week following second dose. Pulmonary embolism 19 days after 2 <sup>nd</sup> dose.                                                                                                                                                                                                                            | 7/-  |
| 4.1(b) | 72/M | Balance disorder, Dizziness, General physical health deterioration, Hemiparesis, Hypoaesthesia, Hyporesponsive to stimuli, Lethargy, Pyrexia, Rash, Respiratory distress                                                                                                                                                  | 4/19 |
| 4.1(b) | 82/M | Anaemia, Dizziness, Fatigue, Gastrointestinal arteriovenous malformation, Gastrointestinal haemorrhage, Haematochezia, Haemoglobin decreased, Internal haemorrhage, Large intestinal haemorrhage, Melaena, Myelodysplastic syndrome, Platelet count decreased, Red blood cell count decreased / multiple chronic diseases | 15/0 |
| 4.1(b) | 82/M | Acute kidney injury, Back pain, Death, Diarrhoea, Dizziness, Hyperkalaemia, Peripheral swelling, Vomiting                                                                                                                                                                                                                 | 56/6 |
| 4.1(b) | 76/F | Death, Dizziness, Headache, Subdural haemorrhage, Thrombocytopenia                                                                                                                                                                                                                                                        | ?/21 |
| 4.1(b) | 39/F | Circulatory collapse, Dizziness, Dyspnoea, Gait disturbance, Nausea / autopsy: heart failure with lipomatosis cordis                                                                                                                                                                                                      | 2/2  |
| 4.1(b) | 90/F | Asthenia, Cerebrovascular accident, Death, Dizziness, Headache, Incorrect dose administered, Somnolence, Vision blurred                                                                                                                                                                                                   | 6/60 |
| 4.1(b) | 52/M | Chills, Death, Decreased appetite, Dizziness, Dyspnoea, Oropharyngeal                                                                                                                                                                                                                                                     | 11/7 |



|  |  |                                                  |  |
|--|--|--------------------------------------------------|--|
|  |  | pain, Pain, Pyrexia / no cause of death reported |  |
|--|--|--------------------------------------------------|--|

In summary, the features of the above deaths do not indicate that dizziness played an important causal role, but rather dizziness was an accompanying symptom to a fatal medical event. These fatal medical events, in turn, have not been causally linked to mRNA-1273

### 3.9 Review of Tinnitus (Vestibular Disorders), with Relevance to mRNA-1273

Tinnitus is the perception of a sound that has no external source. The sensation is commonly described as ringing in the ear, but the sound can be perceived inside or outside the head or predominantly in one or both ears. Qualitative descriptions include humming, tonal ringing, hissing, static, roaring, or a cicada-like sound. Tinnitus can be categorized as objective or subjective. Objective tinnitus — a sound generated within the body by blood flow, muscle contractions, or spontaneous cochlear emissions that can be detected and measured by an external observer — is uncommon. Subjective tinnitus is the more common type of tinnitus. Tinnitus occurs in up to one fourth of adults but is severely bothersome in less than 10%. When bothersome, tinnitus negatively affects sleep, concentration, emotions, and social enjoyment. Population surveys estimate a prevalence of tinnitus of 10 to 25% among persons older than 18 years of age across various nationalities. In population surveys, the sensation is reported to be severely bothersome in only a small percentage of persons with tinnitus (range, 1 to 7%). The prevalence of persistent tinnitus increases with age, reaching a peak among persons in the seventh decade of life, but the prevalence has increased among younger age groups over the past decade, presumably because of increased exposure to damaging recreational noise. Current clinical practice guidelines do not recommend medication for management of the condition. (N Engl J Med 2018; 378:1224-1231 DOI: 10.1056/NEJMcp1506631)

In many cases tinnitus generation is multifactorial; thus, any combination of altered auditory and somatosensory inputs—i.e., hearing loss—together with abnormal activity in central nervous structures (eg, due to traumatic or ischaemic damage or emotional factors) can be relevant for tinnitus generation. Co-occurring psychiatric disorders, such as depression, anxiety, and insomnia, should also be investigated and specifically treated if present, because they play a major part in tinnitus-related impairment of quality of life. (Lancet Neurol 2013; 12: 920–30)

Assessment of the reports of tinnitus received by the MAH is hampered by several important limitations of the data in hand: 1) As noted above in two state-of-the-art medical reviews, tinnitus is a largely a subjective phenomenon and, as such, presents significant diagnostic and therapeutic challenges. 2) The vast majority of the reports received, including those that involve some hearing



loss, do not include complete tinnitus history and comprehensive audiologic evaluation. This could be expected because the above cited NEJM review strongly recommends such evaluation for tinnitus duration greater than six months. 3) The reports of tinnitus mostly occurred in the week following vaccination and thus are frequently accompanied by some of the common signs and symptoms of reactogenicity that can lead to further discomfort, anxiety and possibly also the seeking of medical attention. 4) As noted in the reviews cited above, most patients habituate to tinnitus and are not bothered by it. However, for the reports we have received, adequate time for this to occur had not yet elapsed for many patients.

**Table 15: Cumulative PTs in Association with Tinnitus by Seriousness and Frequency**

| PT                | Non Serious |                   | Serious  |                   | Grand total of # Events | Grand total of % of Total Events |
|-------------------|-------------|-------------------|----------|-------------------|-------------------------|----------------------------------|
|                   | # Events    | % of Total Events | # Events | % of Total Events |                         |                                  |
| Tinnitus          | 2,065       | 22.9%             | 278      | 16.9%             | 2,343                   | 21.9%                            |
| Headache          | 486         | 5.4%              | 41       | 2.5%              | 527                     | 4.9%                             |
| Dizziness         | 347         | 3.8%              | 50       | 3.0%              | 397                     | 3.7%                             |
| Fatigue           | 326         | 3.6%              | 29       | 1.8%              | 355                     | 3.3%                             |
| Nausea            | 258         | 2.9%              | 31       | 1.9%              | 289                     | 2.7%                             |
| Chills            | 257         | 2.8%              | 20       | 1.2%              | 277                     | 2.6%                             |
| Pyrexia           | 244         | 2.7%              | 19       | 1.2%              | 263                     | 2.5%                             |
| Pain              | 193         | 2.1%              | 10       | 0.6%              | 203                     | 1.9%                             |
| Pain in extremity | 172         | 1.9%              | 12       | 0.7%              | 184                     | 1.7%                             |
| Deafness          | 10          | 0.1%              | 147      | 8.9%              | 157                     | 1.5%                             |

For the PT tinnitus there were 2,316 cases (10,680 events) that involved 689 serious cases (1,646 events). There were 2 cases with fatal outcome. A breakdown of the cases reported by gender was 845 males and 1,425 females and 46 unknown, with a mean age of 52 years (SD: 15.0) and a median age of 54 years. For the reporting period, there were 350 serious cases and 793 serious events. There were 2 cases with fatal outcome, zero in the review period.

One case fatality was reported by a consumer and describes the occurrence of suicide in a male patient of an unknown age who received mRNA-1273. No Medical History information was reported. On an unknown date, the patient received dose of mRNA-1273. On an unknown date, the patient committed suicide and ringing in his ears. The patient died on an unknown date. The cause of death was not reported. It is unknown if an autopsy was performed. At the time of death, the outcome of ringing in his ears was unknown. Concomitant medications were not reported. A second case fatality report had essentially the same, limited information as the above report, except that it originated from a health professional rather than a consumer, and likely was another report of the same case.

**Table 16: Distribution of Cumulative Events by First Dose Latency in Association with PT Tinnitus**

|                             | Events | %    |
|-----------------------------|--------|------|
| <b>Latency Since Dose 1</b> |        |      |
| < 7 days                    | 7209   | 67.5 |
| 7 to < 14 days              | 680    | 6.4  |
| 14 to < 30 days             | 681    | 6.4  |
| ≥ 30 days                   | 654    | 6.1  |
| Missing                     | 1456   | 13.6 |

Last dose latency was an average of 4.3 days (SD 8.0). Median latency in days was 2 with a range from zero to 52. There were 10,038 missing values.

The following [Tables-17](#) show that for serious reports including tinnitus, with duration of 7 days or more, most reported that the tinnitus resolved. The three reports in which the tinnitus had not resolved had little clinical commonality with regard to reported non-tinnitus PTs; two reports had onset of tinnitus on the day of vaccination, but the third report had onset 23 days after vaccination.

**Table 17: Tinnitus and Associated Events by Duration**

| Duration Group | Grand total of # Events | Grand total of % of Total Events |
|----------------|-------------------------|----------------------------------|
| ≤01 days       | 428                     | 4.0%                             |
| 02-03 days     | 187                     | 1.8%                             |
| 04-07 days     | 58                      | 0.5%                             |
| 07-29 days     | 101                     | 0.9%                             |

|          |    |      |
|----------|----|------|
| 30+ days | 32 | 0.3% |
|----------|----|------|

### 3.10 Summary

Review of post marketing data shows Dizziness, in P301 trial, potential excess (*4 PBO vs 17 Spikevax*) of treatment-related dizziness after dose 2 at days 1-7. No significant excess in serious, severe or medically attended events were observed. Dizziness is commonly reported after Spikevax administration with typical reactogenicity adverse events. Tinnitus data are inconclusive. Dizziness is commonly reported after Spikevax administration with typical reactogenicity adverse events. Tinnitus reports had similar age distribution to background rates. Few unresolved long duration cases were reported. Co-reported adverse events were typical of reactogenicity and usual tinnitus comorbidity. MedDRA HLT of Inner Ear events primarily involved vertigo. There were no unresolved long duration cases reported. Road Traffic Accidents and Falls with fractures or intracranial hemorrhage were not clearly linked to spikevax. machinery operation accidents were not reported.

## 4 Literature Review

### **Clinical literature search review:**

A literature search was performed 15 July 2021 using PubMed, with the following criteria (Dizziness OR Vertigo OR Tinnitus) AND ( mRNA-1273 OR Moderna COVID vaccine OR COVID vaccine OR COVID-19 vaccine OR COVID OR SARS-CoV-2)

- **Results:** The search returned no case reports, case series or studies.
- **Summary:** No published reports were found that reported cases, case series or studies focusing on dizziness or vertigo or tinnitus in conjunction with mRNA-1273 or another mRNA vaccine against COVID.
- **Conclusion:** Although dizziness has been reported in listings of common adverse events that are considered typical reactogenicity of mRNA vaccines against COVID, neither dizziness, vertigo nor tinnitus has been the focus of reporting or study in relation to these vaccines. With regard to COVID-19 disease, neither tinnitus, vertigo nor dizziness has been clearly shown to be a direct result of SARS-COV-2 infection.

### **4.1 Non-clinical literature search review**

Not applicable

## 5 Discussion

The MAH conducted a signal evaluation of the Validation signal of Dizziness due the signal evaluation was requested by the Medicines and Healthcare products Regulatory Agency (MHRA). During the recent review, MHRA have identified that dizziness is not currently listed in the UK summary of product characteristics (SmPC) for COVID-19 Vaccine Moderna. Dizziness is uncommon and associated with symptoms of reactogenicity. Clinical trial and Postmarketing data shows a minimal imbalance between placebo and mRNA-1273 P301 study cohorts. TEAEs showed more in vaccinees arm; suggestive of early reactogenicity. 3x fold dose after 2<sup>nd</sup> dose and 4x fold after 1<sup>st</sup> dose. No imbalance in serious events or medically attended events. Only increase in 7day after 2<sup>nd</sup> dose suggesting reactogenicity-related events. There were no literature reports of Dizziness following Spikevax/mRNA-1273 were retrieved from the literature search. No significant imbalances were observed with Dizziness associated with Tinnitus (Vestibular Disorders) or Vertigo as data are inconclusive with limited information. The reports of tinnitus mostly occurred in the week following vaccination and thus are frequently accompanied by some of the common signs and symptoms of reactogenicity that can lead to further discomfort, anxiety and seeking of medical attention. Observed to expected analyses showed reporting rates below the background. Fatality associated events were an accompanying symptom not linked causally to vaccine (i.e. cases of suicide and serious chronic diseases such as GBS and alcoholism). Dizziness was statistically significant and is being added to label for adolescent study.

## **6 Conclusion**

Based on this cumulative review, there is evidence to suggest a causal association between mRNA-1273 and Dizziness (Day 1 – 7 after the second dose). Dizziness was considered a validated signal and being added to mRNA-1273 label. Dizziness associated Vestibular Disorders or Vertigo had an insufficient evidence at this time and a causal association between mRNA-1273 cannot be established.

## **7 References**

**20.4.2.2.            Appendix 4b2: Signal Evaluation report: Neuralgic Amyotrophy**



## RESPONSE TO SWISSMEDIC COMMENTS ON CLINICAL/SAFETY RECEIVED ON JUNE 15, 2021

The Sponsor acknowledges SWISSMEDIC comments on CLINICAL/SAFETY topics (in **BOLD**)

### ITEM 1:

#### **Swissmedic Request for Safety Assessment of Neuralgic amyotrophy, 15 Jun 2021**

Swissmedic received one (1) ADR report with PT 'Neuralgic amyotrophy' (4.1(b) ) and one (1) ADR report with PT 'Brachial plexus neuritis' ( ) in a timely relation to the administration of COVID-19 Vaccine Moderna dispersion for injection. Furthermore, one (1) report with PT 'Neuralgic amyotrophy' (4.1(b) ) was reported following 'Covid-19 vaccine' (not further specified), which is currently being assessed by the respective PV centre.

We ask for your position on 'Neuralgic amyotrophy' in connection with the administration of COVID-19 Vaccine Moderna dispersion for injection. Please focus specifically on the frequency (Switzerland versus international), the time course, the 'level of certainty', potential differential diagnoses and necessary measures.

### Sponsor Response:

The company's global safety database was queried for valid, clinical and spontaneous case reports received from Health Care Providers, Health Authorities, consumers and literature, cumulative from 18 December 2020 to 31 May 2021, worldwide, and for Switzerland, reported for the mRNA-1273 vaccine (Moderna COVID-19 vaccine Moderna) using the following Preferred Terms (PTs): "**Neuralgic amyotrophy, Radiculitis brachial, and Brachial plexus injury**". As of 31 May 2021, there have been 250,275,820 doses of the mRNA vaccine distributed worldwide. As of 31 May 2021, there have been 3,980,200 doses of the mRNA vaccine distributed in Switzerland.

A review of the spontaneous reports from the company's global safety database identified, worldwide, 28 case reports with the PTs of Neuralgic amyotrophy, Radiculitis brachial, or Brachial plexus injury. Six out of the 28 cases (21.4%) were considered serious reports, and 22 (78.6%) were considered non-serious (See [Table 1](#)). There was only one (1) case of neuralgic amyotrophy identified for 4.1(b) (4.1(b) ). There were no cases for radiculitis brachial, or brachial plexus injury. The case mentioned by the agency (4.1(b) ) with the PT of brachial plexus neuritis is from a patient from the 4.1(b).

**Table 1. Number and Percentage of Spontaneous Cases of Neuralgic amyotrophy, Radiculitis brachial, and Brachial plexus injury Reported by Seriousness and Preferred Term (PT) for the mRNA-1273 vaccine worldwide. Cumulative to 31 May 2021**

|                        | Non-Serious |                   |         |                  | Serious  |                   |         |                  | Grand total of # Events | Grand total of % of Total Events | Grand total of # Cases | Grand total of % of Total Cases |
|------------------------|-------------|-------------------|---------|------------------|----------|-------------------|---------|------------------|-------------------------|----------------------------------|------------------------|---------------------------------|
| PT                     | # Events    | % of Total Events | # Cases | % of Total Cases | # Events | % of Total Events | # Cases | % of Total Cases | Grand total of # Events | Grand total of % of Total Events | Grand total of # Cases | Grand total of % of Total Cases |
| Neuralgic amyotrophy   | 15          | 0.21%             | 15      | 0.81%            | 3        | 0.04%             | 3       | 0.16%            | 18                      | 0.25%                            | 18                     | 0.98%                           |
| Radiculitis brachial   | 7           | 0.10%             | 7       | 0.38%            | 2        | 0.03%             | 2       | 0.11%            | 9                       | 0.13%                            | 9                      | 0.49%                           |
| Brachial plexus injury | 0           | 0.00%             | 0       | 0.00%            | 1        | 0.01%             | 1       | 0.05%            | 1                       | 0.01%                            | 1                      | 0.05%                           |
| Grand total            | 22          | 0.31%             | 22      | 1.19%            | 6        | 0.08%             | 6       | 0.33%            | 28                      | 0.39%                            | 28                     | 1.52%                           |

Most of the reports (57.1%) involved persons >50 years old (See [Table 2](#)). There were no reports for individuals ≤30 years of age.

**Table 2. Number and Percentage of Spontaneous Cases of Neuralgic amyotrophy, Radiculitis brachial, and Brachial plexus injury Reported by Age for the mRNA-1273 vaccine worldwide. Cumulative to 31 May 2021**

| Age Group          | # Cases   | % Total Cases | # Events  | % of Total Events |
|--------------------|-----------|---------------|-----------|-------------------|
| 18 - 30            | 0         | 0             | 0         | 0                 |
| 31-50              | 10        | 35.7          | 10        | 35.7              |
| 51-64              | 8         | 28.6          | 8         | 28.6              |
| 65-74              | 7         | 25.0          | 7         | 25.0              |
| 75-84              | 1         | 3.6           | 1         | 3.6               |
| Missing            | 2         | 7.1           | 2         | 7.1               |
| <b>Grand total</b> | <b>28</b> | <b>100.0</b>  | <b>28</b> | <b>100.0</b>      |

Most of the reports of Neuralgic amyotrophy, Radiculitis brachial, and Brachial plexus injury concerned females (75%).

**Table 3. Number and Percentage of Spontaneous Cases of Neuralgic amyotrophy, Radiculitis brachial, and Brachial plexus injury Reported by Gender for the mRNA-1273 vaccine worldwide. Cumulative to 31 May 2021**

| Gender | Number | %   |
|--------|--------|-----|
| Male   | 10     | 64  |
| Female | 18     | 36  |
| Total  | 28     | 100 |

The following tables do not include an age category of individuals  $\leq 30$  years as there were no cases reported in that age group.

The majority of the reports (39.2%) had onset of the Neuralgic amyotrophy, Radiculitis brachial, and Brachial plexus injury within seven days following last vaccination (See [Table 4](#)) and most of these reports were in individuals  $>50$  years of age (57%).

**Table 4. Number and Percentage of Spontaneous Cases of Neuralgic amyotrophy, Radiculitis brachial, and Brachial plexus injury Reported by Time-To-Onset (TTO) and Age Group for the mRNA-1273 vaccine worldwide. Cumulative to 31 May 2021**

| TTO by Age           | 31-50 years | %           | 51-64 years | %           | 65-74 years | %           | 75-84 years | %          | Missing  | %          | Grand total | %            |
|----------------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|------------|----------|------------|-------------|--------------|
| 0 to <7 days         | 5           | 17.9        | 1           | 3.6         | 2           | 7.1         | 0           | 0          | 0        | 0          | 8           | 28.6         |
| $\geq 7$ d to <14d   | 2           | 7.1         | 1           | 3.6         | 0           | 0.0         | 0           | 0          | 0        | 0          | 3           | 10.7         |
| $\geq 14$ d and <30d | 1           | 3.6         | 3           | 10.7        | 1           | 3.6         | 0           | 0          | 0        | 0          | 5           | 17.9         |
| $\geq 30$ d          | 0           | 0.0         | 2           | 7.1         | 2           | 7.1         | 0           | 0          | 0        | 0          | 4           | 14.3         |
| Missing              | 2           | 7.1         | 1           | 3.6         | 2           | 7.1         | 1           | 3.6        | 2        | 7.1        | 8           | 28.6         |
| <b>Grand total</b>   | <b>10</b>   | <b>35.7</b> | <b>8</b>    | <b>28.6</b> | <b>7</b>    | <b>25.0</b> | <b>1</b>    | <b>3.6</b> | <b>2</b> | <b>7.1</b> | <b>28</b>   | <b>100.0</b> |

### Observed vs. Expected:

Population based estimates of the incidence of neuralgic amyotrophy typically range from 1-3 cases per 100,000 person-years:

- Netherlands (2015): incidence of 1-3 per 100,000 person-years in a prospective, population-based cohort study<sup>1</sup>
- United States (1985): 1.64 per 100,000 person-years in the population of Rochester, Minnesota<sup>2</sup>

Age stratified estimates by incidence were not identified in the published literature, however a female preponderance has been described.

**Table 5. Observed to expected rates of neuralgic amyotrophy, cases reported through 31 May 2021**

| Outcome                          | Person-years | Observed |      | Expected |      | RR<br>(95% CI)    |
|----------------------------------|--------------|----------|------|----------|------|-------------------|
|                                  |              | Cases    | Rate | Cases    | Rate |                   |
| Neuralgic amyotrophy             |              |          |      |          |      |                   |
| All, Comparison: US [2]          | 8,941,723    | 28       | 0.30 | 146.6    | 1.64 | 0.18 (0.12, 0.28) |
| All, Comparison: Netherlands [1] | 8,941,723    | 28       | 0.30 | 89.4     | 1.00 | 0.30 (0.20, 0.46) |
| All, Comparison: Netherlands [1] | 8,941,723    | 28       | 0.30 | 268.3    | 3.00 | 0.10 (0.07, 0.15) |

When calculating person-time on the basis of a 21-day risk window following each globally administered dose as of 31 May 2021, the observed reporting rate for neuralgic amyotrophy was 0.30 cases per 100,000 person years, which fell below expected rates. Reporting sensitivity as low as 30% would remain consistent with published estimates of the background incidence.

Reported occurrence of neuralgic amyotrophy ranges between 1.6 and 3 cases per 100,000 annually, although actual incidence is likely to be at least 20 to 30 cases per 100,000 individuals secondary to underdiagnosis and recognition<sup>3</sup>. The hereditary form (HNA) is much rarer, with about 200 families known worldwide<sup>4</sup>. Cases have been reported in patients as young as 3 months and as old as 81 years,8,10 but the highest incidence is between the third and seventh decades of life. Males are predominantly affected; ratios range from 1.5:1 to 11.5:1. The cause of neuralgic amyotrophy is still unknown, but autoimmune, genetic, infectious, environmental, and biomechanical processes have been implicated<sup>5</sup>. In idiopathic neuralgic amyotrophy (INA), several antecedent events that may serve as triggers for an immune mediated etiology have been reported. Although this assertion remains to be fully elucidated, available literature suggests that

<sup>1</sup> Alfen, N. van *et al.* Incidence of Neuralgic Amyotrophy (Parsonage Turner Syndrome) in a Primary Care Setting - A Prospective Cohort Study. *Plos One* 10, e0128361 (2015).

<sup>2</sup> Beghi, E., Kurland, L. T., Mulder, D. W. & Nicolosi, A. Brachial plexus neuropathy in the population of Rochester, Minnesota, 1970-1981. *Ann Neurol* 18, 320-323 (1985).

<sup>3</sup> Neuralgic Amyotrophy (Parsonage-Turner Syndrome). Tjoumakaris, Fotios P.; Anakwenze, Oke A.; Kancherla, Vamsi; Pulos, Nicholas. Journal of the American Academy of Orthopaedic Surgeons Publisher: Lippincott Williams & Wilkins

<sup>4</sup> van Alfen N: The neuralgic amyotrophy consultation. *J Neurol* 2007;254(6):695- 704

<sup>5</sup> van Alfen N: Clinical and pathophysiological concepts of neuralgic amyotrophy. *Nat Rev Neurol* 2011;7(6):315-322

possible triggers include, in decreasing order of incidence, viral infections (25% to 55%), immunizations (15%), and the perioperative and peripartum periods (>14%), as well as the period following strenuous exercise (8%)

Evaluation of the reported cases for Neuralgic amyotrophy, Radiculitis brachial, and Brachial plexus injury, shows that the majority of them are from the United States (20; 71.4%) (See [Tables 6 and 7](#)). There was only one (1) report (4.1(b)) with the PT of Neuralgic amyotrophy from 4.1(b). There were no cases reported with the PTs of Radiculitis brachial, and Brachial plexus injury from Switzerland.

**Table 6. Number and Percentage of Spontaneous Cases of Neuralgic amyotrophy by Country of Report for the mRNA-1273 vaccine.  
Cumulative to 31 May 2021**

| Country       | # Cases | %     |
|---------------|---------|-------|
| GERMANY       | 1       | 5.6   |
| NETHERLANDS   | 5       | 27.8  |
| SWITZERLAND   | 1       | 5.6   |
| UNITED STATES | 11      | 61.1  |
| Grand total   | 18      | 100.0 |

**Table 7. Number and Percentage of Spontaneous Cases of Radiculitis brachial, and Brachial plexus injury by Country of Report for the mRNA-1273 vaccine.  
Cumulative to 31 May 2021**

| Country       | # Cases | %   |
|---------------|---------|-----|
| ITALY         | 1       | 10  |
| UNITED STATES | 9       | 90  |
| Grand total   | 10      | 100 |

4.1(b)

This report concerns to the 4.1(b) case reported with the PT of neuralgic amyotrophy, who was a 67 years old male that, 8 days after receiving the 2<sup>nd</sup> dose of the COVID-19 Moderna vaccine, experienced neuralgic shoulder amyotrophy. Six days later the patient was evaluated by orthopedics and he was advised to have a neurological consult, which he had two days later. According to the neurologist, after clinical examination and based on the patient's reports of typical medical history with nocturnal shoulder pain without causal trauma, findings of proximal paresis were suspected to be a neuralgic shoulder amyotrophy. Clinical findings included left scapula more prominent and slightly lateralized. Otherwise trophic and tone normal. Motility intact on all sides, Elevation deficit and mild paresis of the left arm; Shoulder elevation M4+, external rotation M4, otherwise no paresis. Per blood test results, inflammatory/ vasculitic

genesis was ruled out. Concurrent medical conditions included Arterial hypertension, Dyslipidaemia and Drug allergy. Concomitant products included METOPROLOL SUCCINATE (BELOC ZOK) for Arterial hypertension, PRAVASTATIN SODIUM (PRAVASTATIN ACTAVIS) for Dyslipidaemia. At the time of the report, the event of neuralgic amyotrophy (neuralgic shoulder amyotrophy) had not resolved.

**Company assessment:** Based on the WHO-UMC causality assessment this report is considered possible. Based on patient's risk factors (including patient's reports of typical medical history with nocturnal shoulder pain without causal trauma) this report is confounded. However, given the temporal association between the use of the product and the start date of the events, a causal relationship cannot be excluded.

### Discussion and Conclusion:

There were 28 case reports identified worldwide in the MAH global safety database with the PTs of Neuralgic amyotrophy, Radiculitis brachial, and Brachial plexus injury. Six out of the 28 cases (21.4%) were considered serious reports, and 22 (78.6%) were considered non-serious reports. Most of the reports (57.1%) involved persons >50 years old, and females (75%); 39.2% had onset of the events within seven days following last vaccination, and 10 reports were after 1<sup>st</sup> dose, 12 after the 2<sup>nd</sup> dose and 6 unknown dose number.

There was only one report of neuralgic amyotrophy reported in Switzerland; this report is heavily confounded by the patient's medical history of nocturnal shoulder pain with no other information describing how long the patient has suffered from nocturnal shoulder pain. Sometimes this is the only sign of an attack, i.e. with annoying pain in the upper arm lasting a few hours associated with a subsequent loss of pinch grip for a few months. In reports of neuralgic amyotrophy the patient may have suffered from severe pain in both shoulders and arms for weeks on end, and may have a serious orthopnoea requiring nocturnal positive pressure. Patients usually suffer only one attack in their life, but up to 25% may go on to suffer a recurrence. Neuralgic amyotrophy is more common in men (male to female ratio 3 : 2), with an age of onset usually in the second or third decade, but ranging from the neonatal age to the seventh decade<sup>6</sup>.

Based on the WHO-UMC causality assessment there were 14 reports considered conditional (*event or laboratory test abnormality/ more data needed for proper assessment*); 13 reports were considered possible (*event or laboratory test abnormality, with reasonable time relationship to drug intake; could also be explained by disease or other drugs*), and 1 unlikely (*event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible); Disease or other drugs provide plausible explanations*).

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<sup>6</sup> van Alfen, Nens. "The neuralgic amyotrophy consultation." Journal of neurology vol. 254,6 (2007): 695-704. doi:10.1007/s00415-006-0246-4

As noted in the MAH O:E analysis, there is a background rate of neuralgic amyotrophy in the general population. Thus, at least some of the cases of neuralgic amyotrophy following vaccination would have occurred in the absence of vaccination.

As of 31 May of 2021, there have been 250,275,820 doses of the mRNA-1273 vaccine distributed worldwide, and 3,980,200 doses of the mRNA-1273 vaccine distributed in Switzerland. Reporting rate for neuralgic amyotrophy worldwide is 0.1 case per 1 million doses of the mRNA-1273 vaccine distributed; reporting rate of neuralgic amyotrophy for Switzerland is 0.2 cases per 1 million doses of the mRNA-1273 vaccine distributed.

Based on the analysis of all the safety data available as of 31 May 2021, the MAH considers that Neuralgic amyotrophy, Radiculitis brachial, and Brachial plexus injury are not presently a safety issue of concern. The MAH will continue to closely evaluate events of “Neuralgic amyotrophy, Radiculitis brachial, and Brachial plexus injury” using routine surveillance.



**20.4.2.3.            Appendix 4b3: Signal Evaluation report: Erythema Multiforme**



**Signal Evaluation Report**  
  
**for**  
  
**mRNA-1273**  
  
**on**  
  
**Erythema multiforme**

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## List of Abbreviations

|        |                                              |
|--------|----------------------------------------------|
| ADR    | Adverse Drug Reaction                        |
| CDC    | Centers for Disease Control and Prevention   |
| CT     | Clinical Trial                               |
| DLP    | Data Lock Point                              |
| CMQ    | Customized MedDRA query                      |
| EUA    | Emergency Use Authorization                  |
| FDA    | Food and Drug Administration                 |
| HLT    | Higher Level Term                            |
| ICSR   | Individual Case Safety Report                |
| IMP    | Investigational Medicinal Product            |
| MAH    | Marketing Authorization Holder               |
| MedDRA | Medical Dictionary for Regulatory Activities |
| PT     | Preferred Term                               |
| RA     | Regulatory Authority                         |
| SD     | Signal Detection                             |
| SOC    | System Organ Class                           |
| TEAE   | Treatment-emergent adverse event             |
| VAERS  | Vaccine Adverse Event Reporting System       |

## **1 Introduction**

This signal evaluation report provides a detailed analysis on the validity of safety topic on Erythema multiforme in association with the administration of mRNA-1273 in adult patients  $\geq 18$ yo, based on all information available to the MAH at the time of document preparation.

### **1.1 Source of the Signal**

- On 23 July 2021, Moderna received a PRAC request to evaluate a signal of erythema multiforme
- Events of Erythema multiforme (EM) has been intensively monitored by EMA for COVID-19 vaccines as this is considered an AESI. Supportive cases were picked up during monitoring of these events in EudraVigilance.

"As of 21 June 2021, there are 90 cases of EM reported for Spikevax (meanwhile in the 5th MSSR there are only 19 cases of EM (OLP)). Out of 90 cases, 67 cases are from US, 3 from UK, 2 Singapore, 18 from EU.

Taking into consideration the above initial evidence of EM, with cases revealing a plausible temporal association to Spikevax, it is considered that the signal deserves further assessment. It is suggested that the MAH for Spikevax (Moderna Biotech Spain, S.L.) should perform a cumulative review of erythema multiforme. The MAH should discuss the need to update the product information and risk management plan and submit proposals as appropriate."

## 2 Background

**Product:** The MAH has developed mRNA-1273, a novel lipid nanoparticle (LNP)-encapsulated messenger RNA (mRNA)-based vaccine against the 2019 novel coronavirus (CoV; SARS-CoV-2). mRNA-1273, the prototype COVID-19 vaccine, encodes for the full-length spike (S) glycoprotein of the Wuhan-Hu-1 strain of SARS-CoV-2, modified to introduce 2 proline residues to stabilize the S glycoprotein into a prefusion conformation (S-2P). mRNA-1273 consists of an mRNA that is manufactured with LNPs composed of 4 lipids: SM-102, cholesterol, DSPC, and PEG2000-DMG.

**Potential signal:** Erythema multiforme

Erythema multiforme (EM) is immune-mediated, multiple ring or target-like lesions (usually <3cm per lesion, multiple, often starting on hands and feet and moving to trunk, with three concentric color zones – center is dusk/dark with blister or crust, next ring is paler pink, outer ring is bright red), and can be accompanied by mucosal lesions. The lesions usually develop over 3-5 days and resolve in 1-2 weeks, and in some individuals, it may become a recurrent condition. Current theories suggest that a vaccine-induced delayed hypersensitivity results when the antigens are presented on keratinocytes, prompting a CD8+ T cell response (Type IV hypersensitivity). EM is often associated with viral infections, including herpes simplex virus (HSV), and bacterial infections like mycoplasma pneumoniae. EM is also associated with some medications including NSAIDs, statins, sulfonamides, antiepileptics, and antibiotics. Most EM usually resolves within several weeks without sequelae, but some patients have recurring episodes for years. EM usually occurs between the ages of 20-40 y/o, with a slightly higher incidence in males.

Erythema multiforme should be differentiated from Stevens-Johnson Syndrome, toxic epidermal necrolysis, generalized fixed drug eruption, polymorphic exanthematous drug eruptions, and urticaria. Medical review of the post-EUA reports is extremely limited because often neither the description of the lesion nor the clinical details are provided, multiple contradictory PTs are assigned (including urticaria, vaccine reactogenicity or injection site reaction), and no biopsies (definitive diagnosis) are reported. Currently the Brighton Collaboration is developing a case definition for EM (which has been identified as an AESI for COVID vaccines) but is not yet available. The EMA and WHO adopted the International ACCESS Consensus classification of erythema multiforme in the interim

### **3 Review of Data from All Sources**

The assessment of Erythema multiforme in association with the use of mRNA-1273 in all patients exposed was performed using several data sources. The methods of evaluation used in each of the analysed data sources is described below.

#### **3.1 Clinical Trial Data**

The topic of Erythema multiforme was cumulatively reviewed in the MAH safety database with a data-lock point (DLP) of 25 November 2020, searched for any terms including "Erythema multiforme in P301 study. Overall, there were no reports of Erythema multiforme in the clinical trial data.

#### **3.2 External Databases**

No Disproportionate Reporting of Events Using EB05 > 2 (mRNA-1273 versus All vaccines in Adults) in VAERs as of 31 July 2021

#### **3.3 Non-clinical Data**

Not applicable

#### **3.4 Epidemiological studies**

As of 31 July 2021, approximately 206.7 million doses of Spikevac had been administered to 112.4 million individuals in 45 countries, with 67.3% of doses having been administered in the United States. To conduct O/E analyses, total exposed person-time was estimated by assigning a 21-day risk window to each dose. Main analyses did not limit to cases with known latency occurring within 21 days to increase case capture, however sensitivity analyses were also performed limiting to 7, 14 and 21-day risk windows including only cases occurring within the applicable interval. Stratification by age and dose estimated exposure on the basis of the US distribution (<https://covid.cdc.gov/covid-data-tracker/#vaccination-demographic>, Accessed 01 Aug 2021) after capping assumed exposure in individuals 18 years of age at 1% of the total. This cap was added to account for US demographic availability across all products where the Pfizer-BioNTech vaccine is authorized for adolescent use. It should be noted that this may underestimate the total number of individuals that have received Spikevac given that some health authorities have recommended wider spacing of doses than is used in the US.

Population-based studies describing the incidence of erythema multiforme are limited. In the US, where most cases were identified, a 1990 study of the Group Health Collaborative identified an incidence of 4.2 cases per 100,000 person-years<sup>1</sup>. Given that this estimate is similar to a more

recent estimate from the ACCESS project utilizing 2013 data from Denmark (4.04 cases per 100,000 person-years) and that the Danish data included age by gender stratification, this estimate was used to support observed vs. expected analysis. It should be noted, however, that this errs on the side of a conservative analysis as other estimates within databases that appear appropriately capable of ascertaining outpatient events produce estimates ranging from 4 – 15 cases per 100,000 person-years.

Observed vs. expected analyses are shown in Tables 1 and 2. Considering all 143 cases of erythema multiforme (141) or target lesion (3) captured in the database through 31 July 2021, the observed reporting rate was 1.20 cases per 100,000 person-years. A large majority of events occurred after the first dose, however the reporting rate following the first dose remained below expected. Observed rates were at or above the expected in women ages 25-64 years, with the most marked increase seen in women 25-39 years of age. Sensitivity analyses in which it is assumed that only 50% or 25% of cases show similar patterns, noting that the more extreme case of 25% of cases reported is expected to overestimate risk given the selection of a conservative reference rate. Comparisons vs higher rates in ACCESS (e.g. FISABIO) did not produce a similar elevation in adult women.

**Table-3: Observed to Expected, All Cases with a PT of Erythema Multiforme or Target Lesion, Reference Data From Denmark (2013)**

| Outcome          | Person-years | Observed |      | Expected |      | As observed:<br>RR (95% CI) | Assuming 50%<br>of cases were<br>reported: RR<br>(95% CI) | Assuming 25%<br>of cases were<br>reported: RR<br>(95% CI) |
|------------------|--------------|----------|------|----------|------|-----------------------------|-----------------------------------------------------------|-----------------------------------------------------------|
|                  |              | Cases    | Rate | Cases    | Rate |                             |                                                           |                                                           |
| All              | 11,886,387   | 143      | 1.20 | 480.2    | 4.04 | 0.3 (0.25, 0.36)            | 0.6 (0.51, 0.69)                                          | 1.19 (1.06, 1.34)                                         |
| <b>By Age</b>    |              |          |      |          |      |                             |                                                           |                                                           |
| <18              | 118,864      | 2        | 1.68 | 11.2     | 9.43 | 0.18 (0.04, 0.8)            | 0.36 (0.11, 1.12)                                         | 0.71 (0.29, 1.77)                                         |
| 18-24            | 1,069,775    | 11       | 1.03 | 28.1     | 2.63 | 0.39 (0.19, 0.78)           | 0.78 (0.45, 1.37)                                         | 1.56 (0.97, 2.51)                                         |
| 25-39            | 2,496,141    | 51       | 2.04 | 42.9     | 1.72 | 1.19 (0.79, 1.78)           | 2.38 (1.66, 3.39)                                         | 4.75 (3.42, 6.6)                                          |
| 40-49            | 1,782,958    | 23       | 1.29 | 28.2     | 1.58 | 0.82 (0.47, 1.42)           | 1.63 (1.02, 2.61)                                         | 3.27 (2.14, 4.98)                                         |
| 50-64            | 3,209,325    | 35       | 1.09 | 56.5     | 1.76 | 0.62 (0.41, 0.94)           | 1.24 (0.87, 1.76)                                         | 2.48 (1.82, 3.38)                                         |
| 65-74            | 1,901,822    | 11       | 0.58 | 73.4     | 3.86 | 0.15 (0.08, 0.28)           | 0.3 (0.19, 0.48)                                          | 0.6 (0.41, 0.87)                                          |
| 75+              | 1,307,503    | 6        | 0.46 | 27.5     | 2.10 | 0.22 (0.09, 0.53)           | 0.44 (0.22, 0.86)                                         | 0.87 (0.51, 1.51)                                         |
| <b>By Gender</b> |              |          |      |          |      |                             |                                                           |                                                           |
| Male             | 5,610,375    | 40       | 0.71 | 214.6    | 3.82 | 0.19 (0.13, 0.26)           | 0.37 (0.29, 0.48)                                         | 0.75 (0.61, 0.92)                                         |

| Outcome                  | Person-years | Observed |      | Expected |       | As observed:<br>RR (95% CI) | Assuming 50%<br>of cases were<br>reported: RR<br>(95% CI) | Assuming 25%<br>of cases were<br>reported: RR<br>(95% CI) |
|--------------------------|--------------|----------|------|----------|-------|-----------------------------|-----------------------------------------------------------|-----------------------------------------------------------|
|                          |              | Cases    | Rate | Cases    | Rate  |                             |                                                           |                                                           |
| Female                   | 6,276,012    | 102      | 1.63 | 174.1    | 2.77  | 0.59 (0.46, 0.75)           | 1.17 (0.96, 1.43)                                         | 2.34 (1.96, 2.8)                                          |
| <b>By Age and Gender</b> |              |          |      |          |       |                             |                                                           |                                                           |
| <b>Male</b>              |              |          |      |          |       |                             |                                                           |                                                           |
| <18                      | 56,104       | 0        | 0.00 | 6.3      | 11.25 | NA                          | NA                                                        | NA                                                        |
| 18-24                    | 504,934      | 5        | 0.99 | 14.5     | 2.87  | 0.35 (0.12, 0.95)           | 0.69 (0.31, 1.54)                                         | 1.38 (0.7, 2.71)                                          |
| 25-39                    | 1,178,179    | 15       | 1.27 | 23.6     | 2.00  | 0.64 (0.33, 1.22)           | 1.27 (0.74, 2.18)                                         | 2.55 (1.58, 4.1)                                          |
| 40-49                    | 841,556      | 3        | 0.36 | 12.2     | 1.45  | 0.25 (0.07, 0.87)           | 0.49 (0.19, 1.31)                                         | 0.98 (0.44, 2.18)                                         |
| 50-64                    | 1,514,801    | 9        | 0.59 | 32.7     | 2.16  | 0.28 (0.13, 0.58)           | 0.55 (0.31, 0.98)                                         | 1.1 (0.69, 1.77)                                          |
| 65-74                    | 897,660      | 2        | 0.22 | 36.4     | 4.05  | 0.06 (0.01, 0.23)           | 0.11 (0.04, 0.31)                                         | 0.22 (0.1, 0.47)                                          |
| 75+                      | 617,141      | 4        | 0.65 | 18.5     | 2.99  | 0.22 (0.07, 0.64)           | 0.43 (0.19, 0.99)                                         | 0.87 (0.44, 1.69)                                         |
| <b>Female</b>            |              |          |      |          |       |                             |                                                           |                                                           |
| <18                      | 62,760       | 2        | 3.19 | 4.7      | 7.52  | 0.42 (0.08, 2.21)           | 0.85 (0.22, 3.21)                                         | 1.7 (0.54, 5.29)                                          |
| 18-24                    | 564,841      | 6        | 1.06 | 13.4     | 2.38  | 0.45 (0.17, 1.17)           | 0.89 (0.41, 1.94)                                         | 1.79 (0.92, 3.48)                                         |
| 25-39                    | 1,317,963    | 35       | 2.66 | 19.0     | 1.44  | 1.84 (1.05, 3.22)           | 3.69 (2.22, 6.13)                                         | 7.38 (4.57, 11.91)                                        |
| 40-49                    | 941,402      | 20       | 2.12 | 16.3     | 1.73  | 1.23 (0.64, 2.36)           | 2.46 (1.38, 4.37)                                         | 4.91 (2.88, 8.37)                                         |
| 50-64                    | 1,694,523    | 26       | 1.53 | 23.0     | 1.36  | 1.13 (0.64, 1.98)           | 2.26 (1.38, 3.68)                                         | 4.51 (2.87, 7.09)                                         |
| 65-74                    | 1,004,162    | 9        | 0.90 | 36.9     | 3.67  | 0.24 (0.12, 0.51)           | 0.49 (0.28, 0.86)                                         | 0.98 (0.62, 1.55)                                         |
| 75+                      | 690,361      | 2        | 0.29 | 9.1      | 1.32  | 0.22 (0.05, 1.01)           | 0.44 (0.14, 1.42)                                         | 0.88 (0.34, 2.27)                                         |
| <b>By dose</b>           |              |          |      |          |       |                             |                                                           |                                                           |
| Dose 1                   | 6,462,685    | 110      | 1.70 | 261.1    | 4.04  | 0.42 (0.34, 0.53)           | 0.84 (0.7, 1.01)                                          | 1.69 (1.45, 1.96)                                         |
| Dose 2                   | 5,423,703    | 10       | 0.18 | 219.1    | 4.04  | 0.05 (0.02, 0.09)           | 0.09 (0.06, 0.14)                                         | 0.18 (0.13, 0.26)                                         |

\*Rate per 100,000 person-years

Considering only the 29 erythema multiforme cases that were confirmed after clinical review, there were no subgroups that showed an increase in the observed vs. the expected rate. Sensitivity analyses based on a 25% case capture cannot exclude the possibility of an increase, however precision is very poor.

**Table-4: Observed to Expected, Confirmed Cases of Erythema Multiforme, Reference Data From Denmark (2013)**



| Outcome                  | Person-years | Observed |          | Expected |          | As observed: RR (95% CI) | Assuming 50% of cases were reported: RR (95% CI) | Assuming 25% of cases were reported: RR (95% CI) |
|--------------------------|--------------|----------|----------|----------|----------|--------------------------|--------------------------------------------------|--------------------------------------------------|
|                          |              | Cases    | Rate     | Cases    | Rate     |                          |                                                  |                                                  |
| All                      | 11886387     | 29       | 0.243977 | 480.21   | 4.04     | 0.06 (0.04, 0.09)        | 0.12 (0.09, 0.16)                                | 0.24 (0.2, 0.3)                                  |
| <b>By Age</b>            |              |          |          |          |          |                          |                                                  |                                                  |
| <18                      | 118863.9     | 0        | 0        | 11.20886 | 9.43     | NA                       | NA                                               | NA                                               |
| 18-24                    | 1069775      | 6        | 0.560866 | 28.13508 | 2.63     | 0.21 (0.09, 0.51)        | 0.43 (0.22, 0.84)                                | 0.85 (0.49, 1.47)                                |
| 25-39                    | 2496141      | 14       | 0.560866 | 42.93363 | 1.72     | 0.33 (0.18, 0.6)         | 0.65 (0.41, 1.05)                                | 1.3 (0.88, 1.94)                                 |
| 40-49                    | 1782958      | 2        | 0.112173 | 28.17074 | 1.58     | 0.07 (0.02, 0.3)         | 0.14 (0.05, 0.4)                                 | 0.28 (0.13, 0.62)                                |
| 50-64                    | 3209325      | 2        | 0.062318 | 56.48411 | 1.76     | 0.04 (0.01, 0.15)        | 0.07 (0.03, 0.2)                                 | 0.14 (0.07, 0.3)                                 |
| 65-74                    | 1901822      | 4        | 0.210325 | 73.41033 | 3.86     | 0.05 (0.02, 0.15)        | 0.11 (0.05, 0.23)                                | 0.22 (0.13, 0.37)                                |
| 75+                      | 1307503      | 0        | 0        | 27.45755 | 2.1      | NA                       | NA                                               | NA                                               |
| <b>By Gender</b>         |              |          |          |          |          |                          |                                                  |                                                  |
| Male                     | 5610375      | 12       | 0.213889 | 214.5568 | 3.824286 | 0.06 (0.03, 0.1)         | 0.11 (0.07, 0.17)                                | 0.22 (0.16, 0.31)                                |
| Female                   | 6276012      | 16       | 0.254939 | 174.1145 | 2.774286 | 0.09 (0.06, 0.15)        | 0.18 (0.13, 0.27)                                | 0.37 (0.28, 0.49)                                |
| <b>By Age and Gender</b> |              |          |          |          |          |                          |                                                  |                                                  |
| <b>Male</b>              |              |          |          |          |          |                          |                                                  |                                                  |
| <18                      | 56103.75     | 0        | 0        | 6.311672 | 11.25    | NA                       | NA                                               | NA                                               |
| 18-24                    | 504933.7     | 1        | 0.198046 | 14.4916  | 2.87     | 0.07 (0.01, 0.52)        | 0.14 (0.03, 0.61)                                | 0.28 (0.09, 0.84)                                |
| 25-39                    | 1178179      | 8        | 0.679014 | 23.56357 | 2        | 0.34 (0.15, 0.76)        | 0.68 (0.36, 1.28)                                | 1.36 (0.8, 2.31)                                 |
| 40-49                    | 841556.2     | 0        | 0        | 12.20256 | 1.45     | NA                       | NA                                               | NA                                               |
| 50-64                    | 1514801      | 1        | 0.066015 | 32.71971 | 2.16     | 0.03 (0, 0.22)           | 0.06 (0.01, 0.25)                                | 0.12 (0.04, 0.35)                                |
| 65-74                    | 897660       | 2        | 0.222802 | 36.35523 | 4.05     | 0.06 (0.01, 0.23)        | 0.11 (0.04, 0.31)                                | 0.22 (0.1, 0.47)                                 |
| 75+                      | 617141.2     | 0        | 0        | 18.45252 | 2.99     | NA                       | NA                                               | NA                                               |
| <b>Female</b>            |              |          |          |          |          |                          |                                                  |                                                  |
| <18                      | 62760.12     | 0        | 0        | 4.719561 | 7.52     | NA                       | NA                                               | NA                                               |
| 18-24                    | 564841.1     | 5        | 0.885205 | 13.44322 | 2.38     | 0.37 (0.13, 1.04)        | 0.74 (0.33, 1.69)                                | 1.49 (0.75, 2.97)                                |
| 25-39                    | 1317963      | 5        | 0.379373 | 18.97866 | 1.44     | 0.26 (0.1, 0.71)         | 0.53 (0.24, 1.13)                                | 1.05 (0.56, 1.97)                                |
| 40-49                    | 941401.9     | 2        | 0.212449 | 16.28625 | 1.73     | 0.12 (0.03, 0.53)        | 0.25 (0.08, 0.73)                                | 0.49 (0.21, 1.14)                                |

| Outcome        | Person-years | Observed |          | Expected |      | As observed: RR (95% CI) | Assuming 50% of cases were reported: RR (95% CI) | Assuming 25% of cases were reported: RR (95% CI) |
|----------------|--------------|----------|----------|----------|------|--------------------------|--------------------------------------------------|--------------------------------------------------|
|                |              | Cases    | Rate     | Cases    | Rate |                          |                                                  |                                                  |
| 50-64          | 1694523      | 1        | 0.059014 | 23.04552 | 1.36 | 0.04 (0.01, 0.32)        | 0.09 (0.02, 0.37)                                | 0.17 (0.06, 0.5)                                 |
| 65-74          | 1004162      | 2        | 0.199171 | 36.85274 | 3.67 | 0.05 (0.01, 0.23)        | 0.11 (0.04, 0.3)                                 | 0.22 (0.1, 0.47)                                 |
| 75+            | 690361.4     | 0        | 0        | 9.11277  | 1.32 | NA                       | NA                                               | NA                                               |
| <b>By Dose</b> |              |          |          |          |      |                          |                                                  |                                                  |
| Dose 1         | 6462685      | 21       | 0.324942 | 261.0925 | 4.04 | 0.08 (0.05, 0.13)        | 0.16 (0.12, 0.22)                                | 0.32 (0.25, 0.41)                                |
| Dose 2         | 5423703      | 4        | 0.07375  | 219.1176 | 4.04 | 0.02 (0.01, 0.05)        | 0.04 (0.02, 0.07)                                | 0.07 (0.04, 0.12)                                |

### 3.5 Review of the Pharmacovigilance Database

Post marketing data for potential signal of Erythema multiforme was cumulatively reviewed in the MAH Global safety database with a data-lock point (DLP) of 31 July 2021. The term Erythema multiforme was analysed by using the single PT of Erythema multiforme in Medical Dictionary for Regulatory Activities (MedDRA) version 24.0, cases from all sources were included.

### 3.6 Possible Mechanism(s) of Action

Erythema multiforme (EM) is often associated with viral or bacterial infections, especially HSV, drugs and vaccines. The damage to the epithelial cell is through cell-mediated immune (CMI) reaction (delayed hypersensitivity reaction with a risk window of a 2-11 days prior to onset of symptoms). The keratinocyte is the eventual target, with necrosis as early finding. The hypotheses for EM following infection and vaccines share a similar etiology<sup>1</sup>. In the early phase of the disease, the epidermis is infiltrated with CD8 T lymphocytes and macrophages, and these release cytokines, which mediates the inflammatory reaction and resultant apoptosis of keratinocytes.

Some patients have high circulating levels of T-helper cell type 1 (TH1) cytokine response, producing interferon [IFN] gamma, tumor necrosis factor [TNF] alpha, and interleukin [IL] 2, which are proinflammatory cytokines. Vaccine-induced cutaneous hypersensitivity reactions are thought to be due to antigens being expressed on the surface of keratinocytes, leading to a T-lymphocyte immune response against the cells of the epidermis, and ultimately cell death and detachment at the dermoepidermal junction. The specific antigen component that promotes this

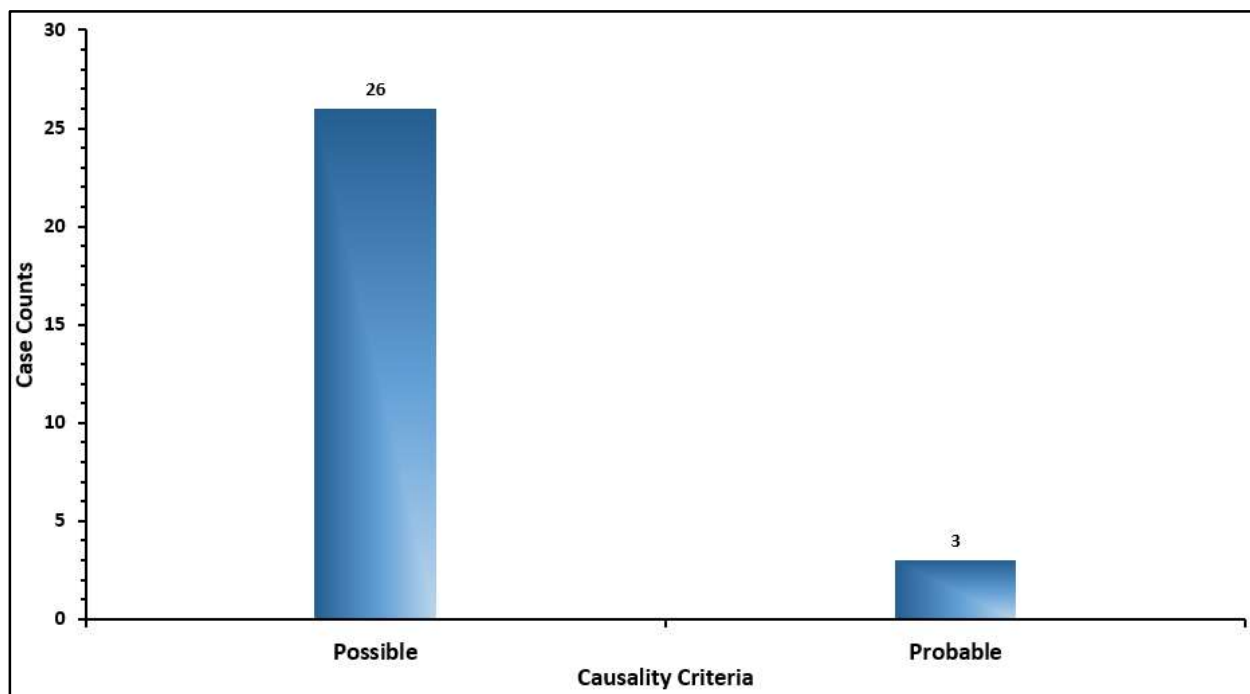
reaction is unknown. Bellavite in 2020<sup>2</sup>, described the problem of multifactorial pathology in causality assessment of adverse events following immunization. He postulated that since most adverse reactions to vaccines occur as excessive inflammatory and immune responses that are associated with various endogenous and exogenous factors, which often interact in complex ways, the current WHO causality assessment could be inadequate in the evaluation of multifactorial diseases.

### 3.7 Results

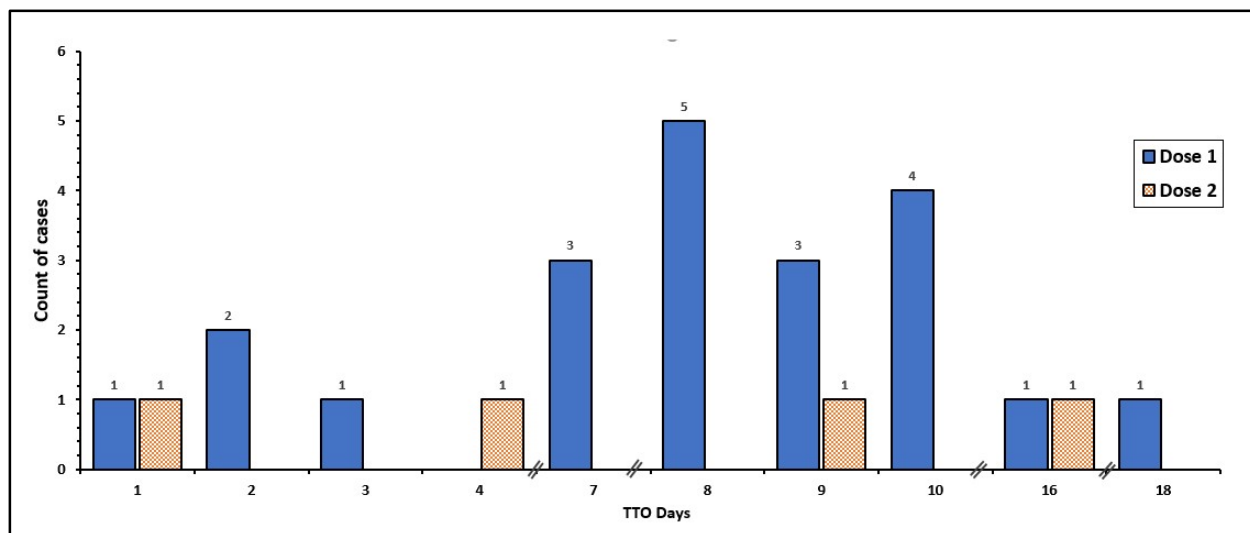
As of the DLP, there were a total of 141 cases with 142 events that involved 133 serious cases (134 events). Of these 124 were medically confirmed. There were 0 cases with fatal outcome. All these 141 cases were reviewed individually using The ACCESS case definition for erythema multiforme, along with the International Consensus classification of erythema multiform and categorized with WHO-UMC causality assessment,

There were 29 confirmed case reports of erythema multiforme. Sixteen cases were reported by females, 12 cases by males and 1 unknown. Two cases were hospitalized. No case fatality was reported. Of the 29 confirmed cases, 22 were erythema multiforme minor and 7 were erythema multiforme major. Using the WHO-UMC causality assessment, there were 26 ‘Possible’ cases and 3 ‘Probable’ (Figure 1). The 26 ‘possible’ cases had concurrent medical conditions such as allergy, diabetes, depression and hypertension. There were on concomitant medications that have been implicated in causing erythema multiforme. (Refer Appendix 1 for detailed causality assessment of all cases). The three ‘probable’ cases had no concurrent medical conditions or concomitant medications, and no risk factors were observed. The time to onset (TTO) of events for 21 cases, was after dose 1, and after dose 2 for 4 cases, and 4 cases had an unknown TTO. (Figure 2). There were no unique patterns or trends seen with the TTO of events that suggests causality by Spikevax vaccine. Appendix-1 have the full narratives of these confirmed cases

#### Figure 1: WHO-UMC Causality Assessment of All Confirmed Cases



**Figure 2: Dose versus Time To Onset (TTO) for 29 Confirmed Cases**



*Dose was unknown for 1 case which is not included in the bar graph of Figure-2*

The tabulated overview of the 29 confirmed cases is as shown in Appendix 1. The mean age of the cases was 39 years (18 – 93years). There were 16 females, 12 males and 1 unknown gender. Majority of these cases were erythema multiforme minor (22, [75.9%]), while 7 cases were erythema multiforme major. Of the 29 cases, 2 cases were hospitalized, but no death was recorded.

Most of the cases occurred after Dose 1 (72.4%), ranging from Day-1 to Day-18. Only 4 cases were reported after Dose 2 and for an unknown dose respectively. For Dose 2, the time interval ranged from Day-1 to Day-16. There was not a typical pattern in time to onset for the reported cases. This is consistent with other types of adverse reports due to reactogenicity, irrespective of causality. The evidence does not show a causal association between Spikevax/mRNA-1273 and events of erythema multiforme. Please see Appendix-2

**Co-reported Adverse events which are presented as MedDRA Preferred Terms (PT),** included arthralgia, myalgia, pharyngitis, pyrexia rash, swelling of the face, hypersensitivity, injection site reactions, fatigue, headache, pain in extremity, vaccination site erythema, vaccination site pain, vaccination site warmth, urticaria, vaccination site induration, pruritus, swelling, warmth, and injection site movement impairment and lymphadenopathy. Refer detailed co-reported PT tabulated in Appendix 1.

**Confounding comorbidities** included hypertension; coronary artery disease; gastroesophageal reflux disease; prostate cancer, diabetes mellitus, food allergy; drug hypersensitivity; migraine; endometriosis; oral allergy syndrome; rhinitis, dermatitis atopic; multiple sclerosis; asthma; and rheumatoid arthritis.

**Concomitant medications:** reports have shown that the following concomitant medications have been associated with erythema multiforme: lotrel, lisinopril, amlodipine, synthroid, montelukast, Zyrtec Allergy; cromoglicate sodium, famotidine, bupropion; citalopram; fexofenadine, omeprazole; pramipexole; teriflunomide; norgestimate and ethinyl estradiol and Tranexamic Acid. (Appendix 2). These confounders provide a more plausible explanation for the occurrence of the event of erythema multiforme.

**Selected Case Summary:** 4.1(b)

This is a case of a 38 year-old-female patient with medical history of multiple sclerosis, GERD, Allergic rhinitis, eczema penicillin allergy, atopic dermatitis and asthma as cofounders and Herpes simplex virus (HSV) infection as the principal risk factor. The patient received the first dose of Spikevax vaccine and 7 days later experienced blisters, dusky, targetoid lesions with peripheral erythematous halo (site of lesions not reported). There were associated edematous oral lesions including herpes simplex, pruritic rash and skin plaque. Lesions later spread to the trunk. Concomitant medications taken by the patient that are implicated with EM included bupropion, citalopram, fexofenadine, estradiol, omeprazole, pramipexole, and teriflunomide. A diagnosis of erythema multiforme major. Grade 3 was made, and the patient was treated with antivirals, topical

steroids, oral antihistamines, and moisturizing cream. Outcome was reported as symptoms resolving at time of report.

Company assessment: This report of erythema multiforme major occurring after receiving the first dose of Spikevax vaccine is confounded by a strong risk factor of HSV infection, concurrent medical history (multiple sclerosis, GERD, Allergic rhinitis, eczema penicillin allergy, atopic dermatitis and asthma) as well as concurrent medications that are currently labeled for erythema multiforme (bupropion, citalopram, fexofenadine, estradiol, omeprazole, pramipexole, and teriflunomide). These confounders provide a more plausible explanation for the occurrence of the event of erythema multiforme. This case is considered WHO Possible.

### **3.8 Possible Risk Factors, due to Gender, Age, and Dose Distribution**

Possible risk factors for erythema multiforme (EM) among the 29 confirmed cases included herpes simplex virus (principal risk factor for EM), drug hypersensitivity, allergies, immunosuppressive conditions such as diabetes mellitus, corticosteroid therapy, cancer, chemotherapy etc. Drugs associated with erythema multiforme include antibiotics like cephalosporins, macrolides, sulfonamides, antipyretics, antidepressants, and seizure medicines. The pattern of background hypersensitivity/allergy and use of multiple medications was observed to be associated with erythema multiforme. Some of the reported cases had history of receiving tetanus vaccine, Hepatitis B vaccine, and human papilloma virus vaccination. Although there has been case reports of erythema multiforme associated with some vaccines, such as DPT/Tdap, Hep B, HPV and Polio, only Hep B vaccine has erythema multiforme in its post market label as an adverse event. Females within age 18 to 68 years, reported more cases. Most case reports occurred after the first dose. Of the 29 confirmed cases, only 4 occurred after dose 2, with an initial peak, which dropped and plateaued at the baseline. This is suggestive more of reactogenicity than delayed hypersensitivity reactions.

## 4 Literature Review

### **Clinical literature search review:**

A literature search was performed 19 July 2021 using PubMed, with the following criteria (“Erythema multiforme”) AND (mRNA-1273 OR Moderna COVID vaccine OR COVID vaccine OR COVID-19 vaccine)

Results: The search returned no case reports, case series or studies.

- **Summary:** Literature search provided no support for an association for an association of mRNA-1273 with Erythema multiforme or vision loss.
- **Conclusion:** Literature search results did not provide evidence of causal association between mRNA vaccines or mRNA-1273 and Erythema multiforme

### **4.1 Non-clinical literature search review:**

Not applicable

## 5 Discussion

The MAH conducted a signal evaluation of the potential signal of Erythema multiforme due to the request from PRAC to evaluate a signal of erythema multiforme

The signal evaluation included a cumulative review of clinical trial data for any terms including "Erythema multiforme" from mRNA-1273 P301 as a 25 November 2020 and review of Erythema multiforme in the MAH safety database with a data-lock point (DLP) of 31 July 2021. There were no reports of Erythema multiforme in clinical trial database.

Post marketing data reported 141 cases with 142 events, of which 29 were confirmed cases. Review of these cases did not show any prominent clinical pattern of occurrence of Erythema multiforme. Many of the reports were medically confirmed. The observed reporting rates of Erythema multiforme are well below background incidence rates and the reported cases require further follow-up to confirm the final diagnosis/etiology. The available data was limited by frequent missing data elements to facilitate full medical review, and absence of clear dechallenge/rechallenge information that is common with vaccine products. There were no trends regarding age and gender. The final outcome was unavailable for the majority of cases so unknown if a final etiology was identified for some of the reported cases. There was no clear temporal association with mRNA-1273 administration and the events reports of Erythema multiforme.



## **6 Conclusion**

Overall, there was no imbalance in clinical trial data. There were no literature reports of Erythema multiforme following Spikevax/mRNA-1273 were retrieved from the literature search. Observed reporting rate for post-marketing data shows no increase in the observed vs. the expected rate. Based on this cumulative review, there is insufficient evidence at this time of a causal association between mRNA-1273 and Erythema multiforme. The evidence does not show a causal association between Spikevax/mRNA-1273 and erythema multiforme. Based on all data reviewed, the signal of erythema multiforme is refuted. The recommendations are no changes to current weekly signal detection process for Spikevax/mRNA-1273 for events of erythema multiforme; and no changes to clinical trial conduct, labeling, other reference safety information or the risk management plan. The topic of Erythema multiforme will be monitored through routine PV activities.

## 7 References

<sup>1</sup> UpToDate. Accessed August 20, 2021. <https://www.uptodate.com/contents/erythema-multiforme-pathogenesis-clinical-features-and-diagnosis>

<sup>2</sup>Bellavite P. Causality assessment of adverse events following immunization: the problem of multifactorial pathology. *F1000Res*. 2020 Mar 9;9:170. doi: 10.12688/f1000research.22600.2. PMID: 32269767; PMCID: PMC7111503.