EMA/CHMP/PRAC/2296/2022
Pharmacovigilance Risk Assessment Committee (PRAC)

# Type II variation assessment report

Procedure No. EMEA/H/C/005735/II/0087

Invented name: COMIRNATY

International non-proprietary name: tozinameran

Marketing authorisation holder (MAH): BioNTech Manufacturing GmbH

This application is in the area of: (Non-)Clinical RMP

eCTD sequences related to the procedure: 0229, 0296

| Status of this report and steps taken for the assessment | | | |
|---|---|---|---|
| **Current step** | **Description** | **Planned date** | **Actual Date** |
| ☐ | Start of procedure | 16 Dec 2021 | 16 Dec 2021 |
| ☐ | PRAC Rapporteur Assessment Report | 03 Jan 2022 | 27 Dec 2021 |
| ☐ | PRAC members comments | 05 Jan 2022 | 05 Jan 2022 |
| ☐ | CHMP members comments | 05 Jan 2022 | 05 Jan 2022 |
| ☐ | Updated PRAC Rapporteur Assessment Report | 06 Jan 2022 | N/A |
| ☐ | Start of written procedure | 11 Jan 2022 | 11 Jan 2022 |
| ☐ | PRAC endorsed relevant sections of the assessment report | 11 Jan 2022 | 11 Jan 2022 |
| ☐ | Request for supplementary information | 13 Jan 2022 | 13 Jan 2022 |
| ☐ | Submission of responses | 09 Feb 2022 | 09 Feb 2022 |
| ☐ | Restart | 10 Feb 2022 | 10 Feb 2022 |
| ☐ | PRAC Rapporteur Assessment Report | 25 Feb 2022 | 25 Feb 2022 |
| ☐ | PRAC members comments | 28 Feb 2022 | 28 Feb 2022 |
| ☐ | CHMP members comments | 28 Feb 2022 | 28 Feb 2022 |
| ☐ | Updated PRAC Rapporteur Assessment Report | 01 March 2022 | N/A |
| ☐ | Start of written procedure | 08 March 2022 | 08 March 2022 |
| ☐ | PRAC outcome | 08 March 2022 | 08 March 2022 |
| ☒ | Opinion | 10 March 2022 | 10 March 2022 |

| Procedure resources | |
|---|---|
| Rapporteur: | Filip Josephson |
| PRAC Rapporteur: | Menno van der Elst |
| Contact person - PRAC Rapporteur | [redacted] |
| Assessor – PRAC Rapporteur | |
| EMA Product Lead | |
| Procedure Assistant | |

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# 1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, BioNTech Manufacturing GmbH submitted to the European Medicines Agency on 15 November 2021 an application for a variation.

The following changes were proposed:

| Variation requested | | Type | Annexes affected |
|---|---|---|---|
| C.I.11.b | C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required | Type II | None |

Submission of an updated RMP version 2.6 to include data from the booster/third dose, including data in patients who have undergone a solid organ transplantation, following the outcomes of procedures EMEA/H/C/005735/II/0062 (third dose in immunocompromise as part of the primary vaccination) and EMEA/H/C/005735/II/0067 (booster dose).

The MAH takes the opportunity to update the RMP regarding the discontinuation of enrollment in study C4591015 (phase 2/3 study to evaluate the safety, tolerability, and immunogenicity in healthy pregnant women 18 years of age and older) and the CSR milestones.

The requested variation proposed amendments to the Risk Management Plan (RMP).

# 2. Overall conclusion and impact on the benefit/risk balance

The MAH BioNTech has submitted a type II variation application for COMIRNATY, COVID-19 mRNA Vaccine to update the RMP to include data from the booster/third dose, including data in patients who have undergone a solid organ transplantation, following the outcomes of procedures EMEA/H/C/005735/II/0062 (third dose in immunocompromise as part of the primary vaccination) and EMEA/H/C/005735/II/0067 (booster dose).

No changes were made to the RMP Summary of Safety Concerns. However the experience of the vaccination campaigns in the Member States shows that Anaphylaxis, while remaining an identified risk for the product, does not have a considerable impact on the risk/benefit balance. The MAH should therefore consider, at the next regulatory opportunity, to reclassify anaphylaxis as not "important", discuss it in the RMP section SVII.2, and remove it from the RMP list of safety concerns. This event is expected to be reported further in summary safety reports (while still required) and in PSURs.

The specific adverse drug reaction follow-up forms for Anaphylactic reaction and VAED have been updated to include rows for additional doses of Pfizer-BioNTech COVID-19 Vaccine or Other COVID-19 Vaccine. In addition, a new Data Capture Aid (follow-up questionnaire) for MIS has been added as routine pharmacovigilance activity, as agreed in the signal procedure Multisystem inflammatory syndrome (MIS) for COVID-19 vaccines (EPITT ref 19732).

To monitor the safety of the booster dose, booster vaccinees should be included in the planned and ongoing PASSs'. Several ongoing and planned PASS' will include an analysis and/or conduct active surveillance of individuals who receive booster dose of the Pfizer-BioNTech COVID-19 vaccine.

No changes were made to the risk minimisation measures.

As discussed and agreed with the Agency, RMP versions v4.0 (approved with procedure EMEA/H/C/005735/X/0077) and v2.6 (ongoing with the underlying variation procedure EMEA/H/C/005735/II/0087) were consolidated to RMP v 4.1 (dated 02 February 2022), later up-versioned to 5.0 without further changes.

The RMP v 5.0 is considered acceptable.

The benefit-risk balance of COMIRNATY, remains positive.

# 3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

| **Variation requested** | | **Type** | **Annexes affected** |
|---|---|---|---|
| C.I.11.b | C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required | Type II | None |

Update of the RMP version 5.0 to include data from the booster/third dose, including data in patients who have undergone a solid organ transplantation, following the outcome of procedures EMEA/H/C/005735/II/0062 (third dose in immunocompromise as part of the primary vaccination) and EMEA/H/C/005735/II/0067 (booster dose).

The MAH took the opportunity to update the RMP regarding the discontinuation of enrollment in study C4591015 (*Phase 2/3 study to evaluate the safety, tolerability, and immunogenicity in healthy pregnant women 18 years of age and older*) and the CSR milestones; and to include the ongoing non-interventional study C4591022 (*Pfizer-BioNTech COVID-19 Vaccine Exposure during Pregnancy: A Non-Interventional Post-Approval Safety Study of Pregnancy and Infant Outcomes in the Organization of Teratology Information Specialists (OTIS)/MotherToBaby Pregnancy Registry*) to address the missing information *Use in pregnancy*.

The MAH also updated the RMP in compliance with the outcome of the Signal of Multisystem inflammatory syndrome (MIS) for COVID-19 vaccines (EPITT ref 19732).

In addition, the MAH consolidated in RMP version 5.0 the updates made in the RMP as part of the approved procedure EMEA/H/C/005735/X/0077.

☒is recommended for approval.

### *Amendments to the marketing authorisation*

The variation requires amendments to the Risk Management Plan.

# 4. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

## *Scope*

Please refer to the Recommendations section above

## *Summary*

Not Applicable

# Annex: Rapporteur's assessment comments on the type II variation

# 5. Introduction

The MAH has submitted a type II variation application for COMIRNATY®, COVID-19 mRNA Vaccine to update the RMP to include data from the booster/third dose, including data in patients who have undergone a solid organ transplantation, following the outcomes of procedures EMEA/H/C/005735/II/0062 (third dose in immunocompromise as part of the primary vaccination) and EMEA/H/C/005735/II/0067 (booster dose).

Please refer to section 8 in this report for the assessment of the Risk Management Plan.

# 6. Risk management plan

The MAH submitted an updated RMP version (v 2.6, date of final sign off 11 November 2021) with this application to align the format and content for the booster dose submission. The amendment will contain single-dose booster (Dose 3) data from Phase 3 C4591001 study participants.

The (main) proposed RMP changes were the following:

| **RMP Part/Module** | **Major Change (s)**<br>**RMP v 2.6** |
|---|---|
| PART I PRODUCT(S) OVERVIEW | |
| | Addition of booster dose |
| PART II SAFETY SPECIFICATION | |
| PART II. Module SI Epidemiology of the Indication(s) and Target Populations | No changes made. |
| PART II. Module SII Non-Clinical Part of the Safety Specification | No changes made. |
| PART II. Module SIII Clinical Trial Exposure | Addition of text and exposure tables from Study C4591001 Phase 3 participants 18 to 55 years who received the BNT162b2 booster.<br><br>Addition of final enrolment numbers of study C4591015. |
| PART II. Module SIV Populations Not Studied in Clinical Trials | Addition of text for booster group in SIV.3 |
| PART II. Module SV Post-Authorisation Experience | Updated with new DLP 30 September 2021 |
| PART II. Module SVI Additional EU Requirements for the Safety Specification | No changes made. |
| PART II. Module SVII Identified and Potential Risks | Addition of data related to booster group for the important risks of anaphylaxis, myocarditis and pericarditis and VAED/VAERD |
| PART II. Module SVIII Summary of the Safety Concerns | No changes made. |
| PART III. PHARMACOVIGILANCE PLAN (INCLUDING POST AUTHORISATION SAFETY STUDIES) | |
| III. 1 Routine Pharmacovigilance activities<br><br>III.2 Additional Pharmacovigilance Activities and<br>III. 3 Summary Table of Additional Pharmacovigilance Activities | Inclusion of the FU questionnaire that was updated to include a specific row for the 3rd dose.<br>Inclusion of the new DCA for MIS/CA<br><br>Inclusion of booster dose analyses/milestones for the following studies: C4591009, C4591012, C4591021, C4591036 and C4591038; milestones updated for C4591015. |
| PART IV. PLANS FOR POST AUTHORISATION EFFICACY STUDIES | |
| | No changes made. |

| RMP Part/Module | Major Change (s)<br>RMP v 2.6 |
|---|---|
| PART V. RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES) | |
| V.1. Routine Risk Minimisation Measures<br><br>V.2. Additional Risk Minimisation Measures<br><br>V.3. Summary of Risk Minimisation Measures | No changes made. |
| PART VI. SUMMARY OF THE RISK MANAGEMENT PLAN | |
| I The Medicine and What It Is Used For<br><br>II Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks | No changes made. |
| PART VII.**Error! Reference source not found.**<br>ANNEXES TO THE RISK MANAGEMENT PLAN | Annex 2: Milestones updated<br>Annex 7: Booster card included<br>Annex 8: Changes to reflect the updated information |

Note that **relevant parts** (e.g. Summary of the safety concerns) including **relevant parts from the RMP covering proposed changes** are reproduced below.

## *6.1. Summary of the safety concerns*

No changes were made to the Summary of Safety Concerns. However, cumulative data from post-marketing use shows that the risk mitigation activities included in the Product Information are well adhere to, and events are managed adequately in clinical practice. Having the experience of the vaccination campaigns in the Member States led the Rapporteur to reconsider the concerns raised at the beginning of the vaccination campaign, when uncertainties on the disruption of medical care due to the pandemic were elevated. The experience shows that Anaphylaxis, while remaining an identified risk for the product, as with any other biologicals, does not have a considerable impact on the risk/benefit balance, therefore the MAH should consider at the next regulatory opportunity to reclassify anaphylaxis as not "important", discuss it in the RMP section SVII.2, and remove it from the RMP list of safety concerns. This event is expected to be reported further in summary safety reports (while still required) and in PSURs.

**Table 1. Summary of Safety Concerns**

| | |
|---|---|
| Important Identified Risks | Anaphylaxis<br>Myocarditis and Pericarditis |
| Important Potential Risks | Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD) |
| Missing Information | Use in pregnancy and while breast feeding |
| | Use in immunocompromised patients |
| | Use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders) |
| | Use in patients with autoimmune or inflammatory disorders |
| | Interaction with other vaccines |
| | Long term safety data |

## 6.2. Pharmacovigilance plan

The changes to this section are indicated in green font, removed text in ~~strike through~~.

**ROUTINE PHARMACOVIGILANCE ACTIVITIES**

Section Routine Pharmacovigilance Activities have been updated with i) Inclusion of the FU questionnaire that was updated to include a specific row for the 3rd dose, ii) Inclusion of the new DCA for MIS/CA.

[...]

Routine pharmacovigilance activities beyond the receipt and review of individual AE reports (e.g. ADRs) include:

- Data Capture Aids have been created for this vaccine. They are intended to facilitate the capture of clinical details about
  - the nature and severity of COVID 19 illness in individuals who have received the COVID-19 mRNA vaccine and is anticipated to provide insight into potential cases of vaccine lack of effect or VAED. The updated version of the DCA is provided in Annex 4;
  - potential anaphylactic reactions in individuals who have received the COVID-19 mRNA vaccine. The updated version of the DCA is provided in Annex 4.
  - potential multisystem inflammatory syndrome in children and adults (MIS-C/A) experienced by individuals following administration of Pfizer-BioNTech COVID-19 Vaccine.
- Additionally, a Pfizer BioNTech COVID-19 Vaccine Follow-up Questionnaire is used for all other reports and is intended to capture more specific information about the 3rd dose, vaccine administration details, facility where vaccine was provided, any prior vaccinations received, medical and family history, adverse events and relevant medical tests.

[...]

**Assessor's comment:**

Annex 4 *Specific adverse drug reaction follow-up forms* of the RMP contains i) *Pfizer-BioNTech COVID-19 Vaccine Anaphylactic Reaction Data Capture Aid*, ii) *Pfizer-BioNTech COVID-19 Vaccine VAED Data Capture Aid*. Both FUQs have been updated to include rows for additional doses of Pfizer-BioNTech COVID-19 Vaccine or Other COVID-19 Vaccine, which is accepted.

As outcome of the Signal of Multisystem inflammatory syndrome (MIS) for COVID-19 vaccines (EPITT ref 19732), PRAC agreed a dedicated questionnaire should be implemented to retrieve an appropriate level of information to facilitate the assessment of cases reporting MIS. Therefore, a new Data Capture Aid for MIS has been added as routine pharmacovigilance activity, which is accepted. However, this new DCA for MIS-C/A is not yet included in Annex 4 of the RMP. The MAH is requested to include the DCA for MIS-C/A in the Annex of the RMP (**OC**).

The MAH states a FUQ is used for all individual reports to gather more specific information (e.g. any prior vaccinations received, medical history, concomitant medication, adverse events etc.) about the 3rd dose. To gather more information about the 3rd dose is considered a routine pharmacovigilance activity. There is no need to include a '3rd dose FUQ' in the RMP (**OC**).

**Monthly Summary Safety Reports**

[...]

**Potential Medication Errors**

This section is applicable to all formulations presented in the RMP.

Large scale public health approaches for mass vaccination may represent changes to standard vaccine treatment process, thereby potentially introducing the risk of medication errors related to: reconstitution and administration, vaccination scheme, storage conditions, errors associated with a multi-dose vial, different formulations, and once other COVID vaccines are available, confusion with other COVID vaccines. These potential medication errors are mitigated through the information in the SmPC and available educational materials for healthcare providers.

- SmPC (section 6.6) contains instructions for reconstitution and administration, vaccination scheme, and storage conditions of the COVID-19 mRNA vaccine.
- A poster with step-by-step instruction for vaccine storage, vial differentiation, dose planning and preparation, and administration is available, which can be conspicuously displayed in settings where vaccine is to be administered for ongoing reference.
- A dosing card which provides information for vaccine storage, vial differentiation, dose planning (including an additional row for the third dose), and administration is available, which is available for healthcare provider reference.
- Brochures for safe handling of the vaccine and dry ice will accompany vaccine shipments.
- Medical information call centers will be available for healthcare providers to obtain information on use of the vaccine.
- Traceability and Vaccination Reminder card (Annex 7) will be provided with the pre-printed manufacturer name, placeholder spaces for dates of vaccinations and batch/lot numbers as a mitigation effort for potential confusion between vaccines. (see Traceability for additional details).

[...]

**Traceability**

[...]

**Cold-chain handling and storage**

[...]

**ADDITIONAL PHARMACOVIGILANCE ACTIVITIES**

The MAA proposes the following 16 studies, of which 3 global, 5 in Europe only, ~~and~~ 7 in US only, ~~and~~ 1 in New Zealand ~~the countries where 1 study is planned to be conducted are not available at this time~~. There are 6 Interventional studies (C4591001, C4591015, BNT162-01 Cohort 13, C4591018, C4591024 and 1 study for vaccine interactions), 2 Low-Interventional studies (WI235284 and WI255886) and 8 Non-Interventional studies (7 safety and 1 effectiveness), summarized in the table below and further detailed in Table 51 (not reproduced here) and Table 52.

| Study Number | Country | Interventional/ Non-Interventional | Purpose |
|---|---|---|---|
| C4591001 | Global | Interventional | Safety |
| C4591015 | Global | Interventional | Safety |
| C4591009 | US | Non-Interventional | Safety |
| C4591010 | EU | Non-Interventional | Safety |
| C4591011 | US | Non-Interventional | Safety |

| Study Number | Country | Interventional/ Non-Interventional | Purpose |
|---|---|---|---|
| C4591012 | US | Non-Interventional | Safety |
| C4591021 (former ACCESS/VAC4EU) | EU | Non-Interventional | Safety |
| C4591038 (former C4591021 substudy) | EU | Non-Interventional | Safety |
| C4591036 (former Pediatric Heart Network) | US | Non-Interventional | Safety |
| C4591014 | US | Non-Interventional | Effectiveness[a] |
| WI235284 | US | Low-Interventional[c] | Effectiveness[a] |
| WI255886 | EU[b] | Low-Interventional[c] | Effectiveness[a] |
| BNT162-01 Cohort 13 | EU | Interventional | Safety |
| C4591018[d] | US | Interventional | Safety |
| C4591024 (former Safety and immunogenicity in high risk adults) | Global | Interventional | Safety |
| C4591030 (Co-administration study with seasonal influenza vaccine) | ~~Not available at this time~~ NZ | Interventional | Safety |

a. Vaccine effectiveness is not a safety concern.
b. United Kingdom.
c. The study does not involve any administration of vaccine or other Pfizer products but since a specimen collection procedure is required per protocol, this qualifies this study as 'low-interventional'.
d. The enrolment into the study became highly problematic after the CDC Advisory Committee on Immunisation Practices (ACIP) recommendation for the prioritization of immunisation of high-risk individuals such as younger adults with high-risk medical conditions including autoimmune disease undergoing immunomodulator treatment (tofacitinib and TNF inhibitors). To address the commitment, (as per procedure PAM-MEA-015) due to the anticipated challenges in the timely enrolment of individuals with rheumatoid arthritis in study C4591018, a decision was made to replace the study C4591018 with increasing the number of immunocompromised participants in study C4591024 to a number comparable to that initially planned across the 2 studies.

**Assessor's comment:**

Table 51 *Additional Pharmacovigilance Activities* (not reproduced here) has been updated as follows.

The following studies will include an analysis and/or conduct active surveillance of individuals who receive booster dose of the Pfizer-BioNTech COVID-19 vaccine:

- Planned non-interventional US PASS C4591009
- Ongoing non-interventional US PASS C4591012
- Ongoing non-interventional EU PASS C4591021 (former ACCESS/VAC4EU)
- Planned non-interventional EU PASS C4591038 (former C4591021 substudy)
- Planned non-interventional US PASS C4591036 (former Pediatric Heart Network Study)

Refer to table 52 below *Summary table of additional PV activities* for milestones Protocol amendment submission (booster dose) of studies C4591009, C4591012 and C4591021 (former ACCESS/VAC4EU).

## III.3 Summary table of additional pharmacovigilance activities (new text in green font)

**Table 2. On-going and Planned Additional Pharmacovigilance Activities**

| **Study (*study short name, and title*)**<br>**Status *(planned/on-going)*** | **Country** | **Summary of Objectives** | **Safety concerns addressed** | **Milestone** | **Due dates** |
|---|---|---|---|---|---|
| **Category 2** | | | | | |
| C4591001<br>*Ongoing* | Global | The objective of the study is to evaluate the safety, tolerability, immunogenicity and efficacy of COVID-19 mRNA vaccine.<br>An imbalance between the vaccine and control groups in the frequency of COVID-19 disease, in particular for severe COVID-19 disease, may indicate the occurrence of vaccine associated enhanced disease. Surveillance is planned for 2 years following Dose 2. | Anaphylaxis<br>Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD)<br>Use in frail patients with co-morbidities (C4591001 subset)<br>Long term safety data. | CSR submission upon regulatory request: | Any time |
| | | | | CSR submission 6 months post Dose 2: | 31-May-2021 |
| | | | | Final CSR submission with supplemental follow-up: | 31-Aug-2023 |

**Table 2. On-going and Planned Additional Pharmacovigilance Activities**

| **Study (*study short name, and title*)**<br>**Status (*planned/on-going*)** | **Country** | **Summary of Objectives** | **Safety concerns addressed** | **Milestone** | **Due dates** |
|---|---|---|---|---|---|
| **Category 3** | | | | | |
| C4591009<br>Planned | US | To assess the occurrence of safety events of interest, including myocarditis and pericarditis, among individuals in the general US population and in subcohorts of interest within selected data sources participating in the US Sentinel System. | Myocarditis and pericarditis<br>AESI-based safety events of interest<br>Use in general population<br>Use in pregnancy<br>Use in immunocompromised patients<br>Use in persons with a prior history of COVID-19 | Protocol submission | 31-Aug-2021 |
| | | | | Protocol amendment submission (booster dose): | 31-Dec-2021 |
| | | | | Monitoring report submission | 31-Oct-2022 |
| | | | | Interim Analysis submission: | 31-Oct-2023 |
| | | | | Final study report submission: | 31-Oct-2025 |
| C4591011<br>*Planned* | US | To assess whether individuals in the US DoD MHS experience increased risk of safety events of interest, following receipt of the COVID-19 mRNA vaccine. | Myocarditis and pericarditis Anaphylaxis<br>AESI-based safety events of interest including vaccine associated enhanced disease<br>Use in pregnancy<br>Use in immunocompromised patients<br>Use in frail patients with co-morbidities (e.g, chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders)<br>Use in patients with autoimmune or inflammatory disorders<br>Long-term safety data. | Interim reports submission: | 31-Dec-2021 |
| | | | | | 30-Jun-2022 |
| | | | | | 31-Dec-2022 |
| | | | | Final CSR submission: | 31-Dec-2023 |
| C4591012<br>*Ongoing* | US | To assess whether individuals in the US Veteran's Affairs Health System | Myocarditis and pericarditis Anaphylaxis | Interim reports submission: | 30-Jun-2021 |
| | | | | | 31-Dec-2021 |

**Table 2. On-going and Planned Additional Pharmacovigilance Activities**

| **Study (*study short name, and title*)**<br>**Status (*planned/on-going*)** | **Country** | **Summary of Objectives** | **Safety concerns addressed** | **Milestone** | **Due dates** |
|---|---|---|---|---|---|
| | | experience increased risk of safety events of interest, following receipt of the COVID-19 mRNA vaccine. | AESI-based safety events of interest including vaccine associated enhanced disease<br>Use in immunocompromised patients<br>Use in frail patients with co-morbidities (e.g, chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders)<br>Use in patients with autoimmune or inflammatory disorders<br>Long-term safety data. | | 30-Jun-2022 |
| | | | | | 31-Dec-2022 |
| | | | | Protocol amendment submission (booster dose): | 30-Nov-2021 |
| | | | | Final CSR submission: | 31-Dec-2023 |

**Table 2. On-going and Planned Additional Pharmacovigilance Activities**

| **Study (*study short name, and title*)**<br>**Status (*planned/on-going*)** | **Country** | **Summary of Objectives** | **Safety concerns addressed** | **Milestone** | **Due dates** |
|---|---|---|---|---|---|
| C4591010<br>*Planned* | EU | To estimate the incidence rates of medically attended safety events of interest (based on the list of AESI) and other clinically significant events among persons vaccinated with the COVID-19 mRNA vaccine and to assess whether these rates elevated relative to estimated expected rates. | Anaphylaxis<br>AESI-based safety events of interest<br>Use in pregnancy<br>Long-term safety data. | Final CSR submission: | 30-Sep-2024 |
| C4591015<br>*Ongoing* | Global | To assess safety and immunogenicity in pregnant women<br><br>In addition, exploratory objectives include:<br>(a) To describe the immune response in infants born to breastfeeding maternal participants vaccinated with prophylactic COVID-19 mRNA vaccine during pregnancy.<br><br>(b) To describe the safety of maternal immunization in infants born to breastfeeding maternal participants vaccinated with prophylactic COVID-19 mRNA vaccine during pregnancy. | Use in pregnancy and while breast feeding. | Final CSR submission: | ~~30-Apr-2023~~<br>31-Mar-2023 |
| C4591014<br>*Planned* | US | To estimate the effectiveness of 2 doses of COVID-19 mRNA vaccine against hospitalisation and emergency department admission for acute respiratory illness due to SARS-CoV-2 infection. | Not Applicable. | Final CSR submission: | 30-Jun-2023 |

**Table 2. On-going and Planned Additional Pharmacovigilance Activities**

| **Study (*study short name, and title*)**<br>**Status (*planned/on-going*)** | **Country** | **Summary of Objectives** | **Safety concerns addressed** | **Milestone** | **Due dates** |
|---|---|---|---|---|---|
| WI235284<br>*Planned* | US[a] | To estimate the effectiveness of 2 doses of COVID-19 mRNA vaccine against hospitalisation for acute respiratory illness due to SARS-CoV-2 infection. | Not Applicable. | Final CSR submission: | 30-Jun-2023 |
| WI255886<br>*Planned* | Ex-EU[a,b] | To estimate the effectiveness of 2 doses of COVID-19 mRNA vaccine against hospitalisation for acute respiratory illness due to SARS-CoV-2 infection. | Not Applicable. | Final CSR submission: | 30-Jun-2023 |
| BNT162-01<br>Cohort 13<br>*Ongoing* | EU | To assess potentially protective immune responses in immunocompromised adults | Use in immunocompromised patients. | IA submission:<br>Final CSR submission: | 30-Sep-2021<br>31-Dec-2022 |
| C4591018<br>*Planned* | US | Safety, immunogenicity over 12 months.<br>Description of COVID-19 cases.<br>RA activity by Clinical Disease Activity Index.<br>N-antigen antibodies for detection of asymptomatic infection. | Use in immunocompromised patients<br>Use in patient with autoimmune or inflammatory disorders. | IA submission: | 31-Dec-2021 |
| C4591024 (former Safety and immunogenicity in high-risk adults)<br>*Planned* | Global | Safety, tolerability and immunogenicity based on representative medical conditions (≥18 years: NSCLC, CLL, in hemodialysis for end-stage renal disease). | Use in immunocompromised patients<br>Use in frail patients with co-morbidities (e.g, chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)<br>Use in patients with autoimmune or inflammatory disorders. | Protocol submission:<br>Final CSR submission: | 30-Jun-2021<br>31-Dec-2022 |

**Table 2. On-going and Planned Additional Pharmacovigilance Activities**

| **Study (*study short name, and title*)**<br>**Status (*planned/on-going*)** | **Country** | **Summary of Objectives** | **Safety concerns addressed** | **Milestone** | **Due dates** |
|---|---|---|---|---|---|
| C4591021 (former ACCESS/VAC4EU)<br>*Ongoing* | EU | Assessment of potential increased risk of adverse events of special interest (AESI) after being vaccinated with COVID-19 mRNA vaccine.<br>Estimating the time trend, in relation to DHPC letter dissemination, of the proportion of individuals who received real-world clinical assessments for myocarditis/pericarditis following Comirnaty vaccination. | Myocarditis and Pericarditis<br>Anaphylaxis<br>AESI-based safety events of interest including vaccine associated enhanced disease<br>Use in pregnancy<br>Use in immunocompromised patients<br>Use in frail patients with co-morbidities (e.g, chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders)<br>Use in patients with autoimmune or inflammatory disorders<br>Long term safety data. | Protocol amendment submission (booster dose) | 31-Dec-2021 |
| | | | | Final CSR submission: | 30-Sep-2024 |
| C4591038 (former C4591021 substudy)<br>*Planned* | EU | To describe the natural history of post-vaccination myocarditis/pericarditis, including recovery status, risk factors, and/or identification of serious cardiovascular outcomes within 1 year of myocarditis/pericarditis diagnosis among individuals vaccinated with BNT162b2 as well as individuals not vaccinated with a COVID-19 vaccine | Myocarditis and Pericarditis<br>Long term safety data | Protocol submission: | 31 January 2022 |
| | | | | Final CSR submission: | 30 September 2024 |
| C4591036 (former Pediatric Heart Network Study) | US | To characterize the clinical course, risk factors, long-term sequelae, and quality of life in children and | Myocarditis and Pericarditis<br>Long term safety data | Protocol submission: | 30-Nov-2021 |

**Table 2. On-going and Planned Additional Pharmacovigilance Activities**

| **Study (*study short name, and title*)**<br>**Status (*planned/on-going*)** | **Country** | **Summary of Objectives** | **Safety concerns addressed** | **Milestone** | **Due dates** |
|---|---|---|---|---|---|
| *Planned* | | young adults <21 years with acute post-vaccine myocarditis | | Final CSR submission: | 31-Oct-2025 |
| C4591030 (Co-administration study with seasonal influenza vaccine)<br>*Planned* | ~~Not available~~ NZ | Safety and immunogenicity of COVID-19 mRNA vaccine and quadrivalent seasonal influenza vaccine when administered separately or concomitantly. | Interaction with other vaccines. | Protocol submission: | 30-Sep-2021 |
| | | | | Final CSR submission: | 31-Dec-2022 |

a. Case-control study nested in a prospective surveillance cohort, conducted as a research collaboration.
b. United Kingdom.

**Assessor's comment:**

Considering EU/EEA is currently experiencing a rising number of infections in the ongoing COVID-19 pandemic, MSs have already started booster dose vaccination campaigns (in addition to continuing efforts to increase full vaccination uptake in individuals who are currently unvaccinated or partially vaccinated). To monitor the safety of the booster dose, booster vaccinees should be included in the planned and ongoing PASSs'.

The following studies will include an analysis and/or conduct active surveillance of individuals who receive ***booster dose*** of the Pfizer-BioNTech COVID-19 vaccine:

- Planned non-interventional US PASS C4591009
- Ongoing non-interventional US PASS C4591012
- Ongoing non-interventional EU PASS C4591021 (former ACCESS/VAC4EU)
- Planned non-interventional EU PASS C4591038 (former C4591021 sub study)
- Planned non-interventional US PASS C4591036 (former Pediatric Heart Network Study)

The protocol amendment submissions (booster dose) of the EU PASS C4591021 (former ACCESS/VAC4EU [due 31 December 2021]) and US PASSs C4591009 (due 31 December 2021), C4591012 (due 30 November 2021) are awaited.

It is not clear why the booster dose is not taken into account in the remaining PASSs' where several safety concerns will be addressed. The MAH is requested to address the booster dose in all PASSs' (**OC**).

**Overall conclusions on the PhV Plan**

The proposed *updated* post-authorisation PhV development plan (per RMP v2.6) is considered sufficient to identify and characterise the risks of the product, provided the request for supplementary information will be adequately addressed.

## *6.3. Risk minimisation measures*

No changes made

## *6.4. Elements for a public summary of the RMP*

No changes made

## *6.5. Annexes*

Annex 2 *Tabulated summary of planned, on-going, and completed pharmacovigilance study programme* has been updated with milestones.

Annex 7: *Other supporting data (including referenced materials)* has been updated with a Booster card

Annex 8: *Summary of changes to the Risk management Plan over time* has been updated to reflect the updated information

**Assessor's comment:**

Annex 7: The Vaccination Card including 1st Dose Date and 2nd Dose Date has been updated with a Booster Dose Date, which is accepted.

The other annexes have been updated appropriately.

### *6.6. Overall conclusion on the RMP*

☒The changes to the RMP could be acceptable provided an updated RMP and satisfactory responses to the request for supplementary information are submitted.

## 7. Request for supplementary information

### *7.1. Other concerns*

#### *RMP aspects*

- The MAH is requested to include the DCA for MIS-C/A in the Annex of the RMP.
- To gather more information (e.g. any prior vaccinations received, medical history, concomitant medication, adverse events etc.) about the 3rd dose is considered a routine pharmacovigilance activity. There is no need to include a '3rd dose FUQ' in the RMP.
- It is not clear why the booster dose is not taken into account in the remaining PASSs' where several safety concerns will be addressed. The MAH is requested to address the booster dose in all PASSs'.

## 8. Assessment of the responses to the request for supplementary information

### *8.1. Other concerns*

#### *RMP aspects*

**Questions**

- The MAH is requested to include the DCA for MIS-C/A in the Annex of the RMP.
- To gather more information (e.g. any prior vaccinations received, medical history, concomitant medication, adverse events etc.) about the 3rd dose is considered a routine pharmacovigilance activity. There is no need to include a '3rd dose FUQ' in the RMP.

- It is not clear why the booster dose is not taken into account in the remaining PASSs' where several safety concerns will be addressed. The MAH is requested to address the booster dose in all PASSs'.

**Summary of the MAH's response**

The MAH updated the RMP v2.6 based on EMA's RfSI received on 13 January 2021 and submits RMP v 4.1 with these responses to RfSI.

The MAH takes this opportunity to consolidate the following RMP versions, as discussed with the Agency:

- RMP v4.0 approved with procedure EMEA/H/C/005735/X/0077
- RMP v2.6 ongoing with the underlying variation procedure EMEA/H/C/005735/II/0087

In addition, the MAH introduces additional updates with RMP v 4.1 as agreed upon with EMA in the bi-weekly meeting on 27th January 2022. The changes are listed in section "Summary of significant changes" in the RMP.

Summary of significant changes in this RMP

| RMP Part/Module | Major Change (s)<br>RMP v 2.6 versus v 4.0 |
|---|---|
| PART I **Error! Reference source not found.** | Addition of booster dose. |
| PART II SAFETY SPECIFICATION | |
| PART II. Module SI Epidemiology of the Indication(s) and Target Populations | No changes made. |
| PART II. Module SII Non-Clinical Part of the Safety Specification | No changes made. |
| PART II. Module SIII Clinical Trial Exposure | Addition of text and exposure tables from Study C4591001 Phase 3 participants 18 to 55 years who received the BNT162b2 booster dose.<br><br>Addition of final enrolment numbers of study C4591015. |
| PART II. Module SIV Populations Not Studied in Clinical Trials | Addition of text for booster dose group in SIV.3 |
| PART II. Module SV Post-Authorisation Experience | Updated with new DLP 30 September 2021 |
| PART II. Module SVI Additional EU Requirements for the Safety Specification | No changes made. |
| PART II. Module SVII Identified and Potential Risks | Addition of data related to booster dose group for the important risks of anaphylaxis, myocarditis, and pericarditis and VAED/VAERD and DLP revised as per table above |
| PART II. Module SVIII Summary of the Safety Concerns | No changes made. |
| PART III. PHARMACOVIGILANCE PLAN (INCLUDING POST AUTHORISATION SAFETY STUDIES) | |
| III. 1 Routine Pharmacovigilance activities<br><br>III.2 Additional Pharmacovigilance Activities<br>and<br>III. 3 Summary Table of Additional Pharmacovigilance Activities | Inclusion of the new DCA for MIS-C and MIS-A<br><br>Inclusion of booster dose analyses/milestones for the following non interventional studies: C4591009, C4591012, C4591010, C4591011, C4591021, C4591036 and C4591038<br><br>Addition of NIS C4591022 |

| RMP Part/Module | Major Change (s) |
|---|---|
| | RMP v 2.6 versus v 4.0 |
| PART IV. PLANS FOR POST AUTHORISATION EFFICACY STUDIES | No changes made. |
| PART V. RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES) | |
| V.1. Routine Risk Minimisation Measures<br><br>V.2. Additional Risk Minimisation Measures<br><br>V.3. Summary of Risk Minimisation Measures | Updated to reflect the preparation of bi-monthly summary safety reports<br><br><br><br>Updated based on the changes made in PART III |
| PART VI. SUMMARY OF THE RISK MANAGEMENT PLAN | |
| I The Medicine and What It Is Used For<br><br>II Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks | No changes made. |
| PART VII.**Error! Reference source not found.** ANNEXES TO THE RISK MANAGEMENT PLAN | Annex 2: Studies/milestones updated<br>Annex 3. Studies updated<br>Annex 4 DCA for MIS-C and MIS-/A<br>Annex 7 Booster dose card included<br>Annex 8: Changes to reflect the updates |

**Assessment of the MAH's response**

RMP v4.1 dated 02 February 2022 was submitted with the response (later up-versioned to 5.0. without further changes), see also table above for the Significant changes to this RMP.

As requested,

- the DCA for MIS-C/A was included in the Annex 4 *Specific Adverse Drug Reaction Follow-up Forms* of the RMP
- a '3rd dose FUQ' has been removed from the RMP. To gather more information (e.g. any prior vaccinations received, medical history, concomitant medication, adverse events etc.) about the 3rd dose is considered a routine pharmacovigilance activity.
- the booster dose will also be addressed in non-interventional safety studies C4591010 and C4591011; overall the booster dose will be addressed in the following non-interventional safety studies: C4591009, C4591012, C4591010, C4591011, C4591021, C4591036 and C4591038

Issue is resolved.

Other minor comments:

1. According to the table Significant changes to this RMP, Part V.1 Routine RMM has been updated to reflect the preparation of bi-monthly summary safety reports. This statement (in the table Significant changes to this RMP) should be moved to Part III.1 Routine PV. Please note that the preparation of bi-monthly summary safety reports has been correctly updated in the RMP.

However, it is suggested to remove the term 'bi-monthly' – and just state *summary safety reports* – in order to prevent similar RMP updates in the future, with the next planned RMP update.

2. As discussed and agreed with the Agency (December 2021) the ongoing non-interventional study C4591022 - *Pfizer-BioNTech COVID-19 Vaccine Exposure during Pregnancy: A Non-Interventional Post-Approval Safety Study of Pregnancy and Infant Outcomes in the Organization of Teratology Information Specialists (OTIS)/MotherToBaby Pregnancy Registry* – was added as additional PV activity to the RMP to address Use in pregnancy (Missing information per RMP).
   This US/Canada study will monitor rates of pregnancy and infant outcomes in planned and unplanned pregnancies exposed to BNT162b2 using an established pregnancy registry. Women receiving BNT162b2 during pregnancy will be followed from exposure to one-year post-partum. Analyses will be conducted to evaluate if the pregnant women receiving the vaccine during pregnancy experience increased risk of pregnancy and infant outcomes compared with 1) pregnant women who are unvaccinated and 2) pregnant women who have received an influenza or tetanus, diphtheria, and acellular pertussis (Tdap) vaccine during pregnancy.
   i. Table 66 *Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern* in part V.3 of the RMP states (note under the table) that studies C4591009, C4591010, C4591011, and C4591021 (former ACCESS/VAC4EU) and C4591022 address only "Use in pregnancy". The MAH is requested to check this statement, since studies C4591009, C4591010, C4591011 and C4591021 also address other safety concerns, with the next planned RMP update.

3. No changes were made to the RMP Summary of Safety Concerns. However the experience of the vaccination campaigns in the Member States shows that Anaphylaxis, while remaining an identified risk for the product, does not have a considerable impact on the risk/benefit balance. The MAH should therefore consider, at the next regulatory opportunity, to reclassify anaphylaxis as not "important", discuss it in the RMP section SVII.2, and remove it from the RMP list of safety concerns. This event is expected to be reported further in summary safety reports (while still required) and in PSURs.

4. Other changes are considered acceptable

**Conclusion**

☒Overall conclusion and impact on benefit-risk balance has been updated accordingly

## Reminders to the MAH

1. The MAH is reminded to submit an eCTD closing sequence with the final documents provided by Eudralink during the procedure (including final PI translations, if applicable) within 15 days after the Commission Decision, if there will be one within 2 months from adoption of the CHMP Opinion, or prior to the next regulatory activity, whichever is first. If the Commission Decision will be adopted within 12 months from CHMP Opinion, the closing sequence should be submitted within 30 days after the Opinion or 5 days after the submission by the MAH of the final language translations, when there is a linguistic review. For additional guidance see chapter 4.1 of the Harmonised Technical Guidance for eCTD Submissions in the EU

2. If the approved RMP is using Rev. 2 of the 'Guidance on the format of the RMP in the EU' and the RMP 'Part VI: Summary of the risk management plan' has been updated in the procedure, the MAH is reminded to provide to the EMA Procedure Assistant by Eudralink a PDF version of the 'Part VI: Summary of the risk management plan' as a standalone document, within 14 calendar days of the receipt of the CHMP Opinion. The PDF should contain only text and tables and be free of metadata, headers and footers.