EMA/PRAC/122656/2022
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC PSUR assessment report

Procedure no.: EMEA/H/C/PSUSA/00010916/202108

Active substance(s): COVID-19 vaccine (Ad26.COV2-S [recombinant]) (COVID-19 Vaccine Janssen)

Period covered by the PSUR: 24/02/2021 To: 24/08/2021

Centrally authorised Medicinal product(s): For presentations: See Annex A	**Marketing Authorisation Holder**
COVID-19 Vaccine Janssen	Janssen-Cilag International N.V.

Status of this report and steps taken for the assessment

Current step	Description	Planned date	Actual Date
☐	Start of procedure:	11 November 2021	11 November 2021
☐	PRAC Rapporteur's preliminary assessment report (AR)	10 January 2022	10 January 2022
☐	MS/PRAC members and MAH comments	9 February 2022	9 February 2022
☐	PRAC Rapporteur's updated assessment report following comments	24 February 2022	24 February 2022
☐	Oral explanation	N/A	N/A
☒	PRAC recommendation	10 March 2022	10 March 2022

Procedure resources	
PRAC Rapporteur	Name: Ulla Wändel Liminga Tel: +46 18 174600 Email: 4.1(b), 4.5
Contact person - PRAC Rapporteur	Name: 4.1(b), 4.5 Tel: +46 18 174600 Email: 4.1(b), 4.5
Assessor – PRAC Rapporteur	Name: 4.1(b), 4.5 Tel: +46 18 174600 Email: 4.1(b), 4.5 Name: 4.1(b), 4.5 Tel: +46 18 174600 Email: 4.1(b), 4.5 Name: 4.1(b), 4.5 Tel: +46 18 174600 Email: 4.1(b), 4.5
Product Lead	Name: 4.1(b) Tel: 4.1(b) Email: 4.1(b)
Procedure Assistant	Name: 4.1(b) Tel: 4.1(b) Email: 4.1(b)

Table of contents

1. Background information on the procedure

This is the assessment of PSUR(s) submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) for COVID-19 vaccine (Ad26.COV2-S [recombinant]) (COVID-19 Vaccine Janssen).

2. Assessment conclusions and actions

This is the first Periodic Safety Update Report (PSUR) for COVID-19 vaccine Janssen (Ad26.COV2.S); covering data for the period from 24 February 2021 to 24 August 2021.

The COVID-19 vaccine Janssen is indicated for active immunisation for the prevention of coronavirus disease-2019 in adults greater than or equal to 18 years of age.

The International birth date (IBD) is 25 February 2021 based on the first authorisation in Bahrain.

An estimated 33,584,049 subjects were administered Ad26.COV2.S worldwide from 25 February 2021 to 31 August 2021. Most of the doses were administered in the US (14,358,641 doses) and in EU/EEA a total of 13,585,015 doses were administered. Germany, Italy, Poland, Portugal and Spain had the highest number of doses administered during this period, but there is a wide variation in number of administered doses in different countries (range 2,412-2,718,200).

The MAH does not suggest any updates of the product information within this procedure.

A number of changes of the product information has been made after the initial EU Commission decision, and during this PSUR period. Those include changes of in the product information related to thrombotic thrombocytopenic syndrome (TTS), Capillary Leak Syndrome (CLS), Guillain-Barré syndrome (GBS) and thrombocytopenia (ITP). Furthermore, lymphadenopathy, diarrhea, dizziness, tinnitus, continuous sensory reactions, and ITP have been added to the product information in the reporting period or shortly after the cut-off date; assessment have been made within various variation procedures.

A number of signals have been reviewed within signal procedures or within the monthly summary safety reports (MSSRs). Those are not replicated in detail in the current PSUR report.

Within the PSUSA, three issues have been assessed in depth; namely flare of autoimmune diseases, autoimmune hepatitis and neuralgic amyotrophy (NA).

Regarding flare of autoimmune diseases, the MAH has provided a cumulative review. Although a biological plausibility behind new onset or/and flares of autoimmune diseases following vaccination against COVID-19 could be possible, potential mechanisms have not been established, and there are no non-clinical/literature data to clearly point at a specific mechanism for such an association for Covid-19 vaccine Janssen.

Based on the case review, it should be acknowledged that there are a number of cases describing flares of different autoimmune diagnosis that are assessed as having at least a possible association with the vaccine, in total 35 cases (e.g., 5 arthritis cases, 7 PSO/PSA cases and 4 SLE cases). On the other hand, in many of the cases presented, the symptoms included arthralgia, myalgia and fever, i.e., common general vaccination reactions rather than a verified true flare in an arthritis. This is an important aspect for the overall assessment. Further, in the two large clinical trials VAC31518COV3001, and VAC31518COV3009, with an approximate 37500 subjects exposed to the vaccine as well as to placebo, there was no significant imbalance with respect to immune-mediated or autoimmune disorders between the two groups. Finally, the number of reported flare cases are considered low in relation to the estimated exposure of the vaccine (approx. 33,584,049 subjects have received the Ad26.COV2.S vaccine worldwide

from launch to 31 August 2021). Although it is not possible to estimate how many of those that could have had an autoimmune disease, it may be assumed that a substantial number of subjects with underlying autoimmune disease can have been exposed to the vaccine since there are no restrictions regarding vaccination in this population. Based on the above, it is agreed with the MAH that there is at present not sufficient support for a causal association between Ad26.COV2.S and flares of autoimmune disorders. Nonetheless, an updated review of flares in autoimmune/inflammatory disorders should be presented with the next PSUR.

Regarding autoimmune hepatitis, the MAH presented a summary of 6 new onset cases which had been identified. The MAH has provided an in-depth evaluation and narrative presentation of these cases as requested in the section request for supplementary information. Based on the narrative description no causal relationship with the vaccine is seen. The MAH is requested to follow this topic with routine pharmacovigilance activities.

Regarding neuralgic amyotrophy, the cumulative review identified 13 spontaneous cases in the global safety database. Of the 13 cases reported, 3 contained medical history, or risk factors that could have contributed to the occurrence of the event. Of the 13 cases, 1 was classified as definite, 1 probable, 4 possible based on the criteria van Alfen 2015. Due to the temporal relationship (event occurring between 1 to 21 days after vaccination), causality was assessed by the MAH as possible for these 6 cases, which can be agreed. The O/E analyses were <1. Despite some cases with a temporal relationship to vaccination, and thereby assessed as possible, it is at this stage agreed that there is insufficient evidence to allow conclusion on causality. With the next PSUR the MAH is requested to present an updated review of cases with neuralgic amyotrophy, with focus on new cases since the current review, and an evaluation, whether the product information needs to be updated

Furthermore, by 20 October 2021, eighteen serious cases of hypertension (on a total of 30 cases of hypertension) have been reported in France. The MAH was requested to present a cumulative review focused on serious hypertension. The MAH has provided a comprehensive analysis of (severe) hypertension comprising a revisit of clinical trial results, cases from the global safety database, cases from the literature and O/E analyses. Based on the provided information it can be concluded that there is insufficient evidence to conclude on a causal relationship between (severe) hypertension and the vaccine.

In the MSSR (EMEA/H/C/005737/MEA/014.4) covering July 2021, a cumulative review of severe cutaneous reactions was provided by the MAH. An update was provided in the PSUR. Based on that, so far, no concerns have been identified. Nevertheless, an updated cumulative review should be presented with the next PSUR.

No RMP update is suggested to be performed with this PSUR which is supported. A number of issues should continue to be followed including current AESI; and as outlined in the latest summary safety report (SSR) evaluation; and be presented in the next PSUR, as well as in upcoming SSRs.

Nevertheless, based on the currently available data, the PRAC rapporteur suggests deleting anaphylaxis from the list of safety concerns (currently important identified risk, listed in the SmPC and PIL) at the next regulatory opportunity.

The benefit/risk balance remains unchanged.

3. Recommendations

Based on the PRAC Rapporteur review of data on safety and efficacy, the PRAC considers that the risk-benefit balance of medicinal products containing Ad26.COV2-S [recombinant]) remains unchanged and

therefore recommends the maintenance of the marketing authorisation(s).

4. Issues to be addressed in the next PSUR

In addition, the MAH(s) should also address the following issues in the next PSUR:

1. In (EMEA/H/C/005737/MEA/014.4) covering July 2021 cumulative review of severe cutaneous reactions was provided by the MAH, and an overview was presented in the current PSUR. So far, no concerns have been identified. Nevertheless, an updated cumulative review should be presented with the next PSUR.
2. The MAH should present an updated review of exacerbation (flare-up) of pre-existing autoimmune/inflammatory disorders in the next PSUR including data from the scientific literature, clinical studies and the post-marketing cases.

   A tabulated case summary of cases that have occurred after the cut off for the review within the current PSUSA should be presented, with the following columns: Case ID, Eudravigilance Case ID, PTs, Patient Age, Patient Gender, First Dose to Onset, Medical History, Concomitant Medications, Case Comment, information dose, WHO causality assessment and the reasoning for the causality category. All available information should be presented to help the review, including time from first dose to onset of the flare-up, time from last dose to onset, medical history (including date first symptoms and current medications, if available.

   In the data presentation and overall discussion, cases from the current review and new cases should be clearly identified, to facilitate the review.

   According to the RMP, "Use in Subjects with Autoimmune or Inflammatory Disorders" will be addressed in two planned observational post authorization safety studies (category 3; VAC31518COV4003 and VAC31518COV4001) with the aim to assess the safety of Ad26.COV2.S vaccine and with final reporting 2024. The MAH should comment on if any interim results regarding use in subjects with autoimmune or inflammatory disorders, especially on flare-ups, from these studies may be available and submit those if possible.
3. With the next PSUR, the MAH is requested to present an updated review of cases with neuralgic amyotrophy, with focus on new cases since the current review, and an evaluation, whether the product information needs to be updated

5. PSUR frequency

☒No changes to the PSUR frequency

The current frequency for submission of 6-month PSURs should remain unchanged.

Annex: updated PRAC Rapporteur assessment comments on PSUR

1. PSUR Data

1.1. Introduction

Ad26.COV2.S is a monovalent vaccine composed of a recombinant, replication-incompetent adenovirus type 26 vector, constructed to encode the severe acute respiratory syndrome coronavirus-2 spike protein.

Ad26.COV2.S is indicated for active immunisation for the prevention of coronavirus disease-2019 in adults greater than or equal to 18 years of age. Ad26.COV2.S is supplied as a colourless to slightly yellow, clear to very opalescent single dose suspension, for intramuscular injection. The indication is as listed in the Company Core Data Sheet and represents the broadest Company-supported use.

No new updates regarding product information have been proposed based on the data provided in this PSUR.

1.2. Worldwide marketing authorisation status

Ad26.COV2.S was first authorized in Bahrain on 25/02/2021 and in the EU on 11/03/2021. AD26.COV2.S is authorised in total 108 countries/territories worldwide (Table 1).

Table 1: List of Countries/Territories

Algeria	Angola	Antigua and Barbuda	Australia	Austria
Bahamas	Bahrein	Benin	Belgium	Belize
Botswana	Brazil	Bulgaria	Burkina Faso	Cabo Verde
Cameroon	Canada	Central African Republic	Chile (WHO)	Colombia
Comoros	Congo	Congo DRC	Côte d'Ivoire	Croatia
Cyprus	Czech Republic	Denmark	Djibouti	Egypt
Estonia	Eswatini	Ethiopia	Finland	France
Gabon	Gambia	Germany	Ghana	Greece
Guatemala	Guinea	Guinea-Bissau	Guyana	Hungary
Iceland	India,	Ireland	Italy	Jamaica
Jordan	Kenya	Korea (Republic of)	Kuwait	Latvia
Lesotho	Liberia	Libya	Liechtenstein	Lithuania
Luxemburg	Madagascar	Malawi	Malaysia	Mali
Malta	Mauretania	Mauritius	Mexico	Moldova
Mozambique	Namibia	Netherlands	New Zealand	Niger
Nigeria	Norway	Panama	Peru	Philippines
Poland	Portugal	Qatar	Romania	Rwanda
Saudi Arabia	Sao Tome and Principe	Senegal	Sierra Leone	Slovakia
Slovenia	South Africa	South Sudan	Spain	Sudan
Sweden	Switzerland	Thailand	Togo	Trinidad and Tobago
Tunisia	Uganda	Ukraine	United Arab Emirates	United Kingdom
United States of America	Vietnam	Zambia		

Key: DRC=Democratic Republic of Congo; WHO=World Health Organisation

Rapporteur assessment comment: AD26.COV2.S is authorised in total 108 countries/territories worldwide. In the EU Ad26.COV2.S was authorized on 11/03/2021.

1.3. Overview of exposure and safety data

1.3.1. Actions taken in the reporting interval for safety reasons

The following significant actions were taken for safety reasons during the period covered by this report (see Table 2).

Table 2: Significant Actions Taken for Safety Reasons During the Reporting Period

Date	Country	Issue	Action Taken
04 Apr 2021	EU/EEA	Reports of a very rare AE involving blood clots in combination with low platelet counts were observed in a small number of individuals following vaccination.	The Company was informed by EMA that a signal concerning embolic and thrombotic events in association with the Janssen COVID-19 vaccine was confirmed by the PRAC Rapporteur.
13 Apr 2021	USA	Reports of a very rare AE involving blood clots in combination with low platelet counts were observed in a small number of individuals following vaccination.	The CDC and the FDA recommended a pause in the use of the Janssen COVID-19 vaccine out of an abundance of caution, effective on 13 Apr 2021.
13 Apr 2021	EU/EEA	Reports of a very rare AE involving blood clots in combination with low platelet counts were observed in a small number of individuals following vaccination.	The Company made the decision to proactively delay the rollout of the vaccine in Europe.
13 Apr 2021 and 19 Apr 2021	ARG, BEL, BRA, CHI COL, DEU, ESP, FIN, FRA, GBR, ITA, JPN, MEX, NLD, PER, PHL, POL, USA, ZAF	Reports of a very rare AE involving blood clots in combination with low platelet counts were observed in a small number of individuals following vaccination.	The Company communicated a voluntary pause of dosing of the vaccine in all ongoing clinical studies.
16 Apr 2021	CAN	Reports of a very rare AE involving blood clots in combination with low platelet counts were observed in a small number of individuals following vaccination.	Health Canada requests the Janssen COVID-19 vaccine label to be updated to include information related to thrombotic events with thrombocytopenia. Label was approved on 23 Apr 2021.
20 Apr 2021	CAN	Reports of a very rare AE involving blood clots in combination with low platelet counts were observed in a small number of individuals following vaccination.	Health Canada requests that the Risk communication relating to thrombotic events and thrombocytopenia be developed and issued concurrently with the label update. Risk communication approved and posted on 26 Apr 2021.
21 Apr 2021	EU/EEA	Reports of a very rare AE involving blood clots in combination with low platelet counts were observed in a small number of individuals following vaccination.	Updated SmPC and PL were submitted to EMA to update Sections 4.4 and 4.8 of the SmPC and Sections 2, 4, and 6 of the PL (Approved on 22 Apr 2021).
23 Apr 2021	USA	Reports of a very rare AE involving blood clots in combination with low platelet counts were observed in a small number of individuals following vaccination.	Final Labeling Fact Sheets for Recipients and Caregivers and the Fact Sheet for Healthcare Providers Administering Vaccine submitted to the FDA. Upon receipt the hold was lifted by the FDA.
22 Apr 2021	ZAF	Reports of a very rare AE involving blood clots in combination with low platelet counts were observed in a small number of individuals following vaccination.	DHCPL in line with the EMA's PRAC review of very rare cases of unusual blood clots with low blood platelets (thrombosis in combination with thrombocytopenia) associated with immunisation with the Janssen COVID-19 vaccine. This was following our notification regarding this safety signal on 13 Apr 2021.

26 Apr 2021	EU/EEA	Reports of a very rare AE involving blood clots in combination with low platelet counts were observed in a small number of individuals following vaccination.	Dissemination of DHPC to inform healthcare professionals that a combination of thrombosis and thrombocytopenia, in some cases accompanied by bleeding, has been observed very rarely following vaccination with the Janssen COVID-19 vaccine.
06 May 2021	EU/EEA	Reports of a very rare AE involving blood clots in combination with low platelet counts were observed in a small number of individuals following vaccination.	Following receipt of final PRAC recommendation, updated EUPI was submitted to the EMA including updates to the warnings and precautions language related to TTS (Approved on 07 May 2021).
07 May 2021	JPN	Reports of a very rare AE involving blood clots in combination with low platelet counts were observed in a small number of individuals following vaccination.	The Company communicated a restart of dosing of the vaccine in all ongoing clinical studies.
07 May 2021	MEX	Reports of a very rare AE involving blood clots in combination with low platelet counts were observed in a small number of individuals following vaccination.	Submitted in the Emergency Use Authorisation request and authorised on 27 May 2021. Reference Country, Document and version: SmPC, Version 42.0.
20 May 2021	EU/EEA	Reports of a very rare AE involving blood clots in combination with low platelet counts were observed in a small number of individuals following vaccination.	Following receipt of final PRAC recommendation, updated EU RMP submitted to EMA. This submission also included a proposed update to the warnings and precautions language related to TTS in the EUPI.
21 May 2021	USA	Theoretical risk of thrombosis with thrombocytopenia in recipients with history of CVST with thrombocytopenia or HIT.	Updated fact sheets were submitted to FDA for review.
25 May 2021	ZAF	Reports of a very rare AE involving blood clots in combination with low platelet counts were observed in a small number of individuals following vaccination.	Distribution of DHPCL concerning risk of thrombosis in combination with thrombocytopenia to HCPs.
27 May 2021	USA	Thrombosis with thrombocytopenia is an Important Identified Risk.	An updated PVP was submitted to the EUA file o include "thrombosis with thrombocytopenia" is an Important Identified Risk.
09 Jun 2021	EU/EEA	Reports of a very rare AE involving blood clots in combination with low platelet counts observed in a small number of individuals following vaccination.	Proposal for updated DHPC for TTS submitted to EMA.
14 Jun 2021	CAN	Reports of a very rare AE involving blood clots in combination with low platelet counts observed in a small number of individuals following vaccination.	Advisement letter received requesting an Amendment to the Interim Order Authorisation for a labelling update related to TTS Warning and Precaution and ADR.
15 Jun 2021	COL	Reports of a very rare AE involving blood clots in combination with low platelet counts observed in a small number of individuals following vaccination.	Proposal of DHCP for TTS submitted to INVIMA.
18 Jun 2021	EU/EEA	Internally identified significant safety issue around cases of CLS.	Emergency safety issue notification to EMA.
18 Jun 2021	ZAF	Internally identified significant safety issue around cases of CLS.	Notified local HA (SAHPRA) of ESI in line with EMA notification.
21 Jun 2021	USA	Internally identified significant safety issue around cases of CLS reported with Ad26.COV2.S.	Notification of the issue to FDA and of potential changes proposed by the Sponsor to the label and Pharmacovigilance Plan and development of DHCP letter.

21 Jun 2021	SAU, KWT, BHR, and QAT	Internally identified significant safety issue around cases of CLS.	Submitted the ESI according to the Safety communication regulations.
25 Jun 2021	USA	Internally identified significant safety issue around cases of CLS.	Submission of Clinical Overview to the FDA which included executive summary for CLS and cumulative review with supportive data, narratives and CIOMS (in accordance with guidance provided by the FDA).
25 Jun 2021	EU/EEA	Internally identified significant safety issue around cases of CLS.	Type 2 variation submitted to EMA to update the EUPI with a contraindication for individuals who have previously experienced episodes of CLS (approved on 09 Jul 2021) and issuance of DHPC for CLS. This DHPC also included updated information related to TTS.
28 Jun 2021	ZAF	TTS and CLS Initial notification of proposed Combined DHCPL sent to local HA (PV unit).	Updated DHCPL regarding TTS Notification of an emerging safety issue (i.e., CLS) was submitted to SAHPRA on 18 Jun 2021.
30 Jun 2021	CAN	Internally identified significant safety issue around the cases of CLS reported with AD26.COV2.S.	Notification of the issue to Health Canada and of potential changes proposed by the Sponsor to the label and development of DHCP letter.
07 Jul 2021	USA	Externally identified significant safety issue around cases of GBS reported with Ad26.COV2.S vaccine.	The FDA required updates to the PL to include a warning statement and associated information regarding GBS following vaccination.
08 Jul 2021	FRA	NITAG limited the use of the vaccine to people over 55 years of age and confirming previous government decision on this limitation.	Restrictions in study population (people over 55 years of age).
08 Jul 2021	USA	Externally identified significant safety issue around cases of GBS reported with Ad26.COV2.S vaccine.	Updated Fact Sheet submission to include a warning statement and associated information regarding GBS following vaccination.
08 Jul 2021	USA	Internal identified significant safety issue around cases of CLS reported with Ad26.COV2.S vaccine.	Based on the FDA feedback the Company included CLS in Section 6.2 Post Authorisation Experience of the Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers).
10 Jul 2021	ZAF	Externally identified significant safety issue around cases of GBS reported with Ad26.COV2.S vaccine.	Notification regarding a significant safety issue pertaining to GBS and the intention of the Company to include a warning and associated information regarding GBS under sections “Warning and Precautions” and “Adverse Reactions”.

12 Jul 2021	EU/EEA	Externally identified significant safety issue around cases of GBS reported with Ad26.COV2.S vaccine.	Type II variation submitted to EMA to update the EUPI to include GBS as an ADR in Section 4.8 and to include related wording in Section 4.4 of the EUPI (approved on 23 Jul 2021).
12 Jul 2021	KOR	Risk management activities for communications to health care professionals (DHPC).	Korea HA, MFDS issued DHPC (safety letter to HCP) for the contraindication to patients with CLS medical history.
12 Jul 2021	BRA	Externally identified significant safety issue around cases of GBS reported with Ad26.COV2.S vaccine.	Communication to local health on cases of GBS reported to VAERS in recipients of the Janssen COVID-19 vaccine. Information supports a plausible causal association between the vaccine and GBS.
18 Jul 2021	QAT, BHR, and KWT	DHPC for "Contraindication in individuals with previous capillary leak syndrome and update on thrombosis with thrombocytopenia syndrome".	Submission of Joint DHPC letter to the HA's for approval.
21 Jul 2021	USA	Internally identified significant safety issue around cases of CLS reported with Ad26.COV2.S vaccine.	Notification of the issue to the FDA and of potential changes proposed by the Company to the label and Pharmacovigilance Plan and development of DHPC letter.
23 Jul 2021	EU/EEA	Post-authorisation experience: Lymphadenopathy, Paraesthesia, Hypoesthesia, Tinnitus, Diarrhoea, and Vomiting.	A Type II variation was submitted to EMA for addition of ADRs.
26 Jul 2021	MEX	Internally identified significant safety issue around cases of CLS reported with Ad26.COV2.S vaccine.	Labeling update submitted on 26 Jul 2021, to the Local Health Authority (COFEPRIS). This update was approved on September 22, 2021. Reference Country, Document and version: EUPI Jul 2021 27 Jul 2021 2021-0006026 (CCDSv006)
27 Jul 2021	JPN	Internally identified significant safety issue around cases of CLS reported with AD26.COV2.S vaccine	Dissemination of DHPC.
28 Jul 2021	USA	Post-authorisation experience: lymphadenopathy, paresthesia, hypoesthesia, tinnitus, diarrhea, and vomiting. Thrombosis and Thrombocytopenia and Anxiety-related Reactions	Fact Sheets updates were submitted for the FDA review, regarding additions to the post-authorisation experience to include lymphadenopathy, paresthesia, hypoesthesia, tinnitus, diarrhea, and vomiting. Additionally, updates were proposed for Section 5.2 Thrombosis and Thrombocytopenia and new text proposed for Section 5.5 Anxiety-related Reactions.
30 Jul 2021	JPN	Reports of GBS.	Dissemination of DHPC.
31 Jul 2021	ZAF	Type II label updates submitted (eCTD seq0002).	Type II label safety updates submitted covering TTS (i.e., CVST/HIT), CLS contraindication and GBS warnings.

01 Aug 2021	SAU	DHPC for "Contraindication in individuals with previous capillary leak syndrome and update on thrombosis with thrombocytopenia syndrome".	Submission of Joint DHPC letter to the SFDA for approval.
02 Aug 2021	ZAF	Distribution of DHCPL on TTS and CLS.	DHCPL letter circulated to HCPs.
03 Aug 2021	EU	Thrombocytopenia as an Important Potential Risk. Propose studies aimed at further characterisation of TTS. GBS as an Important Identified Risk.	An updated EU RMP was submitted to EMA (EMEA/H/C/005737/II/0018).
05 Aug 2021	MEX	Externally identified significant safety issue around cases of GBS reported with Ad26.COV2.S Janssen COVID-19 vaccine.	Labeling update submitted on 05 Aug 2021, to the Local Health Authority (COFEPRIS). This update was approved on 22 Sep 2021. Reference Country, Document and version: EUPI Jul 21 27 Jul 2021 2021-0006026 (CCDSv006)
11 Aug 2021	UAE	DHPC for "Contraindication in individuals with previous capillary leak syndrome and update on thrombosis with thrombocytopenia syndrome".	Submission of Joint DHPC letter to the UAE HA for approval.

Key: ADR=Adverse Drug Reaction; AE=Adverse Event; ARG=Argentina; BEL=Belgium; BHR=Bahrain; BRA=Brazil; CAN=Canada; CCDS=Company Core Data Sheet; CHI=Chile; CIOMS=Council for International Organisation of Medical Sciences; CLS=Capillary Leak Syndrome; COL=Colombia; CDC=Center for Disease Control and Prevention; COVID-19= Coronavirus Disease-2019; CVST=Cerebral Venous Sinus Thrombosis; DEU=Germany; DHPC=Direct Healthcare Professional Communication; DHPCL=Dear Healthcare Provider Communication Letter; EMA=European Medicines Agency; ESI=Emerging Safety Issue; ESP=Spain; EU=European Union; EUA: Emergency Use Authorisation; EU/EEA=European Union/ European Economic Area; EU PI=European Union Product Information; EU RMP=European Union Risk Management Plan; FDA=Food and Drug Administration; FIN=Finland; FRA=France; GBS=Guillain-Barré Syndrome; GBR=Great Britain; HA=Health Authority; HCP=Health Care Professional; HIT=Heparin Induced Thrombocytopenia; ITA=Italy; JPN=Japan; KOR=Korea (Republic of); KWT=Kuwait; MEX=Mexico; MFDS=Ministry of Food and Drug Safety; NLD=Netherlands; PER=Peru; PHL= Philippines; PL=Package Leaflet; POL=Poland; PRAC=Pharmacovigilance Risk Assessment Committee; PV=Pharmacovigilance; PVP=Pharmacovigilance Plan; QAT=Qatar; SAHPRA=South African Health Products Regulatory Authority; SAU=Saudi Arabia; SFDA=Saudi Food and Drug Authority; SmPC=Summary of Product Characteristic; SSI=Safety Signal Investigation; TTS=Thrombosis With Thrombocytopenia Syndrome; UAE=United Arab Emirates; USA=United States of America; VAERS=Vaccine Adverse Event Reporting System; ZAF=South Africa.

Rapporteur assessment comment: Actions taken for safety reasons during the period covered by this report in EU/EEA are shown in the Table above.

1.3.2. Changes to reference safety information

The CCDS contains the Company Core Safety Information (CCSI). The CCDS in effect at the end of the reporting period is dated 12 July 2021. The significant changes to the CCDS (i.e., CCSI) made by the MAH within the reporting interval are listed in Table 3.

Table 3: Significant Changes to the Ad26.COV2.S CCDS During the Reporting Period

CCDS Version and Date	CCDS Section	Description of Change(s)
CCDS v001 03 Feb 2021	---	New CCDS
CCDS v002 20 Apr 2021	Adverse Reactions	Addition of anaphylaxis to the Adverse Reactions section.
CCDS v002 20 Apr 2021	Adverse Reactions Post-marketing data	Addition of the post-marketing adverse reaction TTS
CCDS v002 20 Apr 2021	Warnings and Precautions \	Addition of a Warning concerning TTS
CCDS v003 13 May 2021	Adverse Reactions, Clinical Efficacy and CMC	Optional changes to align Adverse Reactions (in structure and format), Clinical Efficacy and CMC sections with approved EU and US sections.
CCDS v004 17 May 2021	Warnings and Precautions	Update to the Warning and Precaution for TTS to include patients with a history of CVST and HIT.
CCDS v005 23 Jun 2021	Contraindications	Addition of contraindication for patients that have previously experienced Capillary Leak Syndrome.
CCDS v006 12 Jul 2021	Adverse Reactions Post-marketing Data	Addition of post-marketing adverse reactions for Lymphadenopathy, Paraesthesia, Hypoesthesia, Guillain Barré Syndrome, Tinnitus, Diarrhoea, and Vomiting.
CCDS v006 12 Jul 2021	Adverse Reactions	Correction to figures for Headache in Table 3: Solicited Systemic Adverse Reactions Reported in the 7 days Following Vaccination–Individuals 18 to 59 years of age.
CCDS v006 12 Jul 2021	Warnings and Precautions	Addition of Anxiety related reactions.
CCDS v006 12 Jul 2021	Warnings and Precautions	Addition of Guillain Barré Syndrome.
CCDS v006 12 Jul 2021	Warning and Precautions	Update to TTS Warning: • Unusual sites for thrombosis • Cases occurring in the first 3 weeks • Clinical course of TTS resembling HIT • Investigation for 3 weeks following vaccination if a patient presents with thrombosis or thrombocytopenia • Use of heparin in patients with TTS may be harmful

Key: CCDS=Company Core Data Sheet; CMC=Chemistry, Manufacturing, and Controls; CVST=Cerebral Venous Sinus Thrombosis; EU=European Union; HIT=Heparin Induced Thrombocytopenia; TTS=Thrombosis with Thrombocytopenia; US=United States.

Rapporteur assessment comment:

The information that has been updated in the CCDS is in agreement to the updates that has occurred in the product information in EU during the period covered by this report.

1.3.3. Estimated exposure and use patterns

Cumulative subject exposure in clinical trials

The cumulative subject exposure in clinical trials was up to 24 August 2021. Overall, an estimated 78,231 healthy subjects have been enrolled in the Ad26.COV2.S clinical program, of which approx. 62,358 subjects have received Ad26.COV2.S in the Company-sponsored interventional clinical trials (see Table 4). Of these, 580 subjects were exposed to Ad26.COV2.S in the Phase 1 trials, 5,935 subjects were exposed to Ad26.COV2.S in a Phase 1/2a trial, 6,993 subjects were exposed to Ad26.COV2.S in the Phase 2 trial, and over 59,850 subjects were exposed to Ad26.COV2.S in the Phase 3 trials. Additionally, 16,142 subjects were exposed to Ad26.COV2.S in the pre-approval access programs.

Table 4: Estimated Cumulative Subject Exposure From Clinical Trials

Treatment	Number of Subjects
Ad26.COV2.S	62,358
Comparator	N/A
Placebo	38,397

Key: N/A= Not Applicable.
Number of subjects exposed to at least 1 study vaccine, recorded in the study databases up to cut-off date.
Trials included VAC31518COV1001, VAC31518COV1002, VAC31518COV1003, VAC31518COV2001, VAC31518COV2008, VAC31518COV3001, VAC31518COV3003, and VAC31518COV3009.
The number of subjects exposed to study vaccine in blinded trials (VAC31518COV2001 [Adolescents], VAC31518COV3003, and VAC31518COV2008) are estimates.
A total of 22,524 subjects (482 subjects from Trial VAC31518COV1001; 149 subjects from Trial VAC31518COV2001; 13,855 subjects from Trial VAC31518COV3001; and 8,038 subjects from Trial VAC31518COV3009) that received a regimen with both Ad26.COV2.S and placebo, subjects are counted for both Ad26.COV2.S and placebo.

Cumulative and interval patient exposure from marketing experience

Estimates of exposure are based upon the number of administered doses reported from Centers for Disease Control and Prevention (CDC [2021]) for the United States, European Centre for Disease Prevention and Control (ECDC [2021a]) for European Economic Area countries, Korea Disease Control and Prevention Agency (KDCA [2021]) for South Korea, and Ministério da Saúde (2021) for Brazil.

Interval/Cumulative exposure estimates

As this is the first PBRER for Ad26.COV2.S, both the interval and cumulative exposure data are the same. The interval/cumulative subject exposure for Ad26.COV2.S from 25 Feb. 2021 to 31 Aug. 2021 is provided in Table 5. The end date of the exposure data (31 Aug. 2021) was selected to be in alignment with available data.

Table 5: Interval/Cumulative Subjects Exposure to Ad26.COV2.S From 25 February 2021 to 31 August 2021

Region/Country	Number of Subjects Exposed/ Number of Administered Doses[a]
EEA	
Austria	250,852
Belgium	349,565
Bulgaria	132,464
Croatia	64,454
Cyprus	19,292
Czechia	191,949
Denmark	48,040
Estonia	44,554
France	990,858
Germany	2,718,200
Greece	367,897
Hungary	135,704
Iceland	53,107
Ireland	230,163
Italy	1,415,759
Latvia	105,724
Lithuania	166,702
Luxembourg	34,870
Malta	19,438
Netherlands	786,420
Norway	2,412
Poland	1,743,057
Portugal	1,076,949
Romania	566,646
Slovakia	62,463
Slovenia	82,917
Spain	1,924,559
ROW	
Brazil	4,435,504
South Korea[b]	1,204,889
US	**14,358,641**
Total	**33,584,049**

Key: CDC=Centers for Disease Control and Prevention, ECDC=European Centre for Disease Prevention and Control, EEA=European Economic Area; KDCA=Korea Disease Control and Prevention Agency; ROW=Rest of World; US=United States.

a: Number of vaccine doses administered were reported from CDC for the US, from ECDC for EEA countries, from KDCA for South Korea and from Ministério da Saúde for Brazil.

b: Vaccine administration data is available from 10 June 2021 onwards.

Rapporteur assessment comment:

An estimated 33,584,049 subjects were administered Ad26.COV2.S worldwide from 25 February 2021 to 31 August 2021. Most of the doses were administered in the US (14,358,641 doses) and in EU/EEA; 13,585,015. Germany, Italy, Poland, Portugal and Spain had the highest number of doses administered during this period.

Patient exposure by age for Ad26.COV2.S in EEA

Age stratifications are based upon the number of administered doses available for EEA which is provided using the data from ECDC (2021b; Table 6). Other stratifications are unavailable such as: sex, usage in pregnant or breastfeeding women, usage in hepatic impairment population, and usage in renal impairment population.

Table 6: Interval/Cumulative Subjects Exposure by Age Group in EEA (25 February 2021 to 31 August 2021)

Country	Age Groups (Years)[a]						
	18 to 24	25 to 49	50 to 59	60 to 69	70 to 79	≥80	Age Unspecified
Austria	42,103	130,817	43,835	19,312	9,588	6,089	
Belgium	52,643	164,899	72,325	25,406	13,035	18,925	-
Bulgaria	9,888	70,342	26,124	16,261	7,920	2,444	25
Croatia	7,119	35,674	13,157	8,186	3,045	1,759	3
Cyprus	2,694	11,686	3,668	1,136	295	130	
Czechia	16,096	74,913	34,347	40,778	24,699	7,356	
Denmark	5,393	41,991	507	122	47	8	
Estonia	5,969	26,388	6,208	3,256	1,330	1,724	624
Greece	79,587	208,742	50,832	19,333	8,213	9,218	3,018
Hungary	15,337	75,280	25,417	14,872	5,454	2,188	-
Iceland	12,548	36,182	3,782	834	220	44	-
Ireland	81,875	66,598	73,579	9,443	702	152	45
Italy	95,353	377,024	368,527	423,995	145,387	12,846	
Latvia	9,741	49,579	21,228	14,645	7,087	5,150	-
Lithuania	17,430	91,146	35,583	18,813	6,061	3,405	15
Luxembourg	6,826	17,391	7,465	2,886	359	193	
Malta	5,763	22,097	1,838	453	80	79	-
Poland	221,554	1,077,028	239,489	157,418	38,577	12,289	29,163
Portugal	234,204	518,268	229,589	80,594	24,148	6,911	2
Romania	55,476	315,437	112,340	73,212	35,486	11,688	
Slovakia	9,848	38,134	11,156	5,456	1,907	687	
Slovenia	10,954	50,791	13,564	7,178	2,923	890	
Spain	66,580	890,967	574,304	232,337	149,900	19,427	-
Total	**1,064,981**	**4,391,374**	**1,968,864**	**1,175,926**	**486,463**	**123,602**	**32,895**

Key: EEA=European Economic Area
a: Data by age group is not available for France, Germany, Netherlands, and Norway.

Rapporteur assessment comment: Age stratifications based upon the number of administered doses available for EEA shows that most of the doses were administered in the age groups younger than 69 years of age. However, data is not available for France, Germany, the Netherlands and Norway. In these countries almost 5,000,000 doses were administered and thereby summarised data on exposure by age group could be different if these countries were included.

1.3.4. Data in summary tabulations

The MAH has provided cumulative and interval summary tabulations of adverse events following immunization received cumulatively to the data lock date of this PSUR (25-Feb-2021 to 24-Aug-2021).

These AEFI are derived from non-interventional post-marketing studies, other solicited sources, and spontaneous notification, including reports from healthcare professionals, consumers, scientific literature, and regulatory authorities and reported as:

- Interval and cumulative number of reports (overall)
- Interval and cumulative number of reports per System Organ Class (SOC)
- Interval and cumulative number of reports, stratified by seriousness

Rapporteur assessment comment:

At the time of data lock point, most of cases originated from the US followed by the EEA cumulatively, and from the EEA followed by the US in the current interval.

Cumulatively, 185,405 events were reported (30,792 serious events: 185,405 non-serious events).

The most frequently reported spontaneous AEs were in the SOCs: General disorders and administration site conditions (cumulatively 75,040 thereof 5,681 serious), nervous system disorders (cumulatively 31,633 thereof 5,727 serious) and musculoskeletal and connective tissue disorders (cumulatively 23,735 thereof 1,806 serious).

1.3.5. Findings from clinical trials and other sources

Ongoing clinical trials

An "ongoing clinical trial" is by the MAH defined as a trial in which the first Informed Consent Form (ICF) has been signed, whether a hold is in place or analysis is complete, but for which a final CSR is not available at the DLD for this PBRER, regardless of whether the last subject last visit has occurred. A brief summary of all ongoing clinical trials is presented below.

- Trial VAC31518COV1001: A Phase 1/2a, randomised, double-blind (d-b), placebo-controlled (p-c), first-in-human, multicentre trial in adults aged 18 to 55 years (y) inclusive and adults aged 65 y and older to evaluate the safety, reactogenicity, and immunogenicity of Ad26.COV2.S at 2 dose (d) levels, administered IM as a single-d or 2-d schedule, with a single booster vaccination administered in 1 cohort. There were no important emerging safety findings identified.
- Trial VAC31518COV1002: A Phase 1, randomised, d-b, p-c trial in adults aged ≥20 to ≤55 y and ≥65 y in good health with or without stable underlying conditions in Japan to evaluate the safety, reactogenicity, and immunogenicity of Ad26.COV2.S at 2 d levels, administered IM as 2 d schedule. There were no important emerging safety findings identified.
- Trial VAC31518COV1003: A Phase 1, randomised, observer-blind, parallel-group trial to compare the safety, reactogenicity, and immunogenicity of Ad26.COV2.S at a single d of $5x10^{10}$ virus particles in 2 different volumes in healthy adults aged ≥18 to ≤65 y. There were no important emerging safety findings identified.
- Trial VAC31518COV2001: A Phase 2a, randomised, d-b, p-c, multicentre trial to evaluate a range of dose levels and vaccination intervals of Ad26.COV2.S in healthy adults aged 18 to 55 y inclusive and adults aged 65 y and older and to evaluate 2 d levels of Ad26.COV2.S in healthy adolescents aged 12 to 17 y inclusive. There were no important emerging safety findings identified.
- Trial VAC31518COV2008: A Phase 2, randomised, d-b, parallel, multicentre trial to assess the reactogenicity, safety, and immunogenicity of a booster dose of Ad26.COV2.S in adults ≥18 y, who have previously received a primary vaccination with Ad26.COV2.S or BNT162b2. There were no important emerging safety findings identified.
- Trial VAC31518COV3001: A Phase 3, randomised, d-b, p-c, multicentre, pivotal trial to evaluate the efficacy, safety, and immunogenicity ofAd26.COV2.S for the prevention of severe acute respiratory syndrome coronavirus 2 spike (SARS-CoV-2) mediated COVID-19 in adults aged 18 y and older. There were no important emerging safety findings identified.
- Trial VAC31518COV3003: A Phase 3, randomised, d-b trial to evaluate 6 d levels of Ad26.COV2.S administered as a 2-d schedule in healthy adults aged 18 to 55years, inclusive. In this trial, the safety, reactogenicity, and immunogenicity of Ad26.COV2.S of 1 d (d 1 of the 2-d regimen) and 2 d of Ad26.COV2.S will be evaluated. There were no important emerging safety findings identified.
- Trial VAC31518COV3009: A Phase 3, randomised, d-b, p-c, multicentre trial to assess the efficacy, safety, and immunogenicity of Ad26.COV2.S for the prevention of SARS-CoV-2 mediated COVID-19 in adults aged 18 y and older. There were no important emerging safety findings identified.

Rapporteur assessment comment: Based on review of the data for the 8 ongoing MAH sponsored clinical trials included in this report for Ad26.COV2.S, no new safety signal was identified during the reporting period. Please note that after the DLP for this PSUSA; further detailed review of updated data from 3001 and 3009 have been undertaken regarding thromboembolism.

Independent Data Monitoring Committee/Data Safety Monitoring Board

During the reporting period, no safety related recommendations were received from Independent Data Monitoring Committee/Data Safety Monitoring Board meetings.

Long-term Follow-up

No long-term follow-up information became available during the reporting period.

Other Therapeutic Use of Medicinal Product

During the reporting period, 1 pre-approval access program (VAC31518COV4006) was completed, and 1 pre-approval access program (VAC31518COV4007) was ongoing. No clinically important safety information from these programs that follow a specific protocol (solicited reporting as per International Council for Harmonisation [ICH] E2D) was identified.

Findings from non-interventional studies

Based on review of the data from non-interventional study (VAC31518COV4005) during the reporting period, no new information with a potential impact to the benefit-risk assessment has been identified.

Information from other clinical trials and sources

Other Clinical Trials

During the reporting period, 3 non-MAH sponsored interventional studies were ongoing: 1 interventional clinical study (VAC31518COV2009) sponsored by University Hospital Southampton National Health Service (NHS) Foundation Trust, 1 interventional clinical study (VAC31518COV3012 [Sisonke {Together}]) sponsored by South African Medical Research Council, and 1 interventional clinical study (DMID 21-0012) sponsored by National Institutes of Health (NIH). The summary and safety findings from these studies are presented in short below:

- Study VAC31518COV2009 (in short): Phase 2, randomised, multicentre study being conducting in the United Kingdom to determine reactogenicity and immunogenicity of booster vaccination against ancestral and novel variants of SARS-CoV-2. During the PBRER reporting period, no relevant safety information related to Ad26.COV2.S from this clinical study became available.
- Study VAC31518COV3012 (Sisonke [Together]) (in short): A Phase 3b, open-label, single-arm, multicentre, implementation study to monitor the effectiveness of the single dose Ad26.COV2.S among health care workers at least 18 y of age as compared to the general unvaccinated population in South Africa. During the reporting period, no new relevant safety findings related to Ad26.COV2.S from this clinical study became available.
- Study DMID 21-0012 (in short). A Phase 1/2, open-label study in healthy individuals, 18 y of age and older, with no known history of COVID-19 or SARS-CoV-2 infection. This study is designed to assess the safety, reactogenicity, and immunogenicity of a delayed (>12 weeks) vaccine boost on a range of Emergency Use Authorisation dosed COVID-19 vaccines (mRNA-1273 Moderna; BNT162b2 Pfizer/BioNTech; or Ad26.COV2.S). At the time of DLD of this PBRER, 150 subjects received Ad26.COV2.S in this study. During the reporting period, no relevant safety information related to Ad26.COV2.S from this clinical study became available.

Rapporteur assessment comment:
There is no relevant safety information that became available from completed non-interventional studies and from Other Clinical Trials of Ad26.COV2.S during the reporting period.

Medication errors

The Company global safety database was searched for medically confirmed and medically unconfirmed cases, received during this reporting period, which coded to the Standardised MedDRA Query (SMQ) Medication errors (broad). During this reporting period, 1,385 (912 medically confirmed and 473 medically unconfirmed) cases reporting medication error were identified. Of these 1,385 cases, 110 were serious and 1,275 were nonserious reporting a total of 1,811 events (21 serious, 1,790 nonserious). Of the 1,385 cases, 4 were from placebo-controlled studies, 2 from open-label studies, and 1,379 from post-marketing sources (including spontaneous and solicited cases).

A frequency distribution of 1,811 MedDRA PTs of interest involving the use of Ad26.COV2.S in these 1,385 cases is provided in Table 8.

Table 8: Frequency Distribution of MedDRA PTs of Interest in Cases Involving Use of Ad26.COV2.S and Reporting Medication Errors (Events=1,811)

MedDRA PTs	Number of Events[a]
Poor quality product administered	366
Product storage error	303
Product administered to patient of inappropriate age	261
Expired product administered	138
Incorrect route of product administration	117
Underdose	101
Incorrect dose administered	85
Medication error	74
Product administration error	62
Extra dose administered	37
Inappropriate schedule of product administration	37
Product use issue	32
Product temperature excursion issue	30
Overdose	24
Wrong technique in product usage process	19
Accidental exposure to product	17
Wrong product administered	15
Needle issue	14
Syringe issue	14
Product administered at inappropriate site	13
Product dispensing error	9
Vaccination error	6
Accidental overdose	5
Interchange of vaccine products	3
Product label issue	3
Product dose omission issue	3
Product use in unapproved indication	2
Incorrect dose administered by device	2
Incorrect product administration duration	2
Occupational exposure to product	2
Product packaging issue	2
Circumstance or information capable of leading to medication error	1
Device malfunction	1
Drug delivery system malfunction	1
Exposure via skin contact	1
Incomplete course of vaccination	1
Intercepted product administration error	1
Intercepted medication error	1
Multiple use of single-use product	1
Product name confusion	1
Product label confusion	1
Product preparation issue	1
Product barcode issue	1
Product prescribing error	1
Total Events	**1,811**

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term.
a: A single case may report more than 1 MedDRA PT of interest.

Of the 1,385 cases retrieved, 374 reported the PT of *Off label use*, 2 *Product use in unapproved indications*, 261 in *Product administered in patient of inappropriate age*, and 117 in *Incorrect route of product administration*.

During this reporting period, 4 cases reporting medication error were retrieved from placebo-controlled studies (VAC31518COV3001 (n=2), VAC31518COV3009 (n=2)). These 4 cases reported 4 PTs of Overdose (n=3), and Device malfunction (n=1), 1 reported no AE and in the other 3 cases the additional relevant AEs reported were acute respiratory failure, depression, intracranial aneurysm, cerebral ischaemia, ruptured cerebral aneurysm, cerebral vasoconstriction, meningitis bacterial, vasospasm, subarachnoid haemorrhage, and hydrocephalus. The mean and median TTO for EOI was 132 days and 134.5 days, respectively. The outcome for the EOI were fatal (n=1) and resolved (n=3). EOI causality was reported as: Company/reporter as not related (n=4).

During this reporting period, 2 cases reporting medication error were retrieved from an open-label study. These 2 cases were from VAC31518COV4007-Brazil Early Access and reported 2 nonserious PTs of Underdose (n=1) and Wrong technique in product usage process (n=1

During this reporting period, 1,379 cases reporting medication error were retrieved from post-marketing sources and reported a total of 1,805 EOIs (17 serious, 1,788 nonserious). Age range was 12 to 97 y. Most of the cases referred to errors regarding storage and/or administration of the vaccine. Review of the cases largely showed that either the vaccine was administered after being at room temperature for more than 6 hours, was stored incorrectly, or was drawn from a punctured vial kept beyond the recommended storage time.
A number of reports pertained to patients who received 2 dose of Ad26.COV2.S or to patients who received different vaccine types against COVID-19. A total of 116 cases documented incorrect route of administration and where reported the routes were: intravenous (n=87), subcutaneous (n=18), topical (n=2). these 116 cases were Most of medically not confirmed (n=97). Two hundred seventy-six (n=276) cases referred to use in adolescents (n=273) or children (n=3, all with age unspecified).

Most cases involved errors without harm; no AEs were reported in 1,024 of the 1,379 cases with medication errors. Of the 355 cases who reported an AE, 259 were nonserious. The most frequently reported events in these nonserious cases represented local or systemic reactogenicity to Ad26.COV2.S. Of the 96 serious cases with AEs, 71 were medically unconfirmed. The safety profile of Ad26.COV2.S in the 96 cases was consistent with the safety profile in the overall population vaccinated with Ad26.COV2.S. The reported mean and median TTO for the EOI was 1.2 days and 0 day, respectively. Where reported (n=63), the outcomes for the EOI were resolved (n=32), not resolved (n=26), and resolving (n=5).

Rapporteur assessment comment: Evaluation of the data on medication error received for Ad26.COV2.S during the reporting period did not identify patterns of medication errors and/or potential medication error suggestive of new safety concerns.

Medication errors in paediatric cases
During this reporting period, 276 cases reporting medication error were retrieved in paediatric patients, all from post-marketing sources (128 medically confirmed and 148 medically unconfirmed).

Most of the cases (88%) reported as *product administered to patient of inappropriate age*. Of these 276 cases, 9 were serious and 267 were nonserious reporting a total of 293 EOI (2 serious, 291 nonserious).

These 276 cases reported PTs of *Product administered to patient of inappropriate age* (n=257), *Product use issue* (n=19), Underdose (n=9); *Wrong product administered*, *Poor quality product administered*, *Product use in unapproved indication* (n=2 each); and *Accidental exposure to product and Medication error* (n=1 each). The age range was 12 to 17 y, most of the cases referring to adolescents (n=273). No AEs were reported in most of the cases (n=200). In the remaining 76 cases, 7 of the cases were serious

and concerned patients who experienced dyspnoea and throat tightness (n=1), vaccination failure (n=1), anaphylactic reaction (n=3), manifestation of systemic reactogenicity, including pyrexia (n=1) and loss of consciousness. No new safety concern arose from review of these paediatric cases.

Rapporteur assessment comment: Cases of product use in a limited number of children have been reported. No new safety issues were identified through review of these paediatric cases. Evaluation of the data on medication error received for Ad26.COV2.S during the reporting period did not identify patterns of medication errors and/or potential medication error suggestive of new safety concerns.

Product-Specific Literature

Abbattista M, Martinelli I, Peyvandi F. Comparison of adverse drug reactions among four COVID-19 vaccines in Europe using the EudraVigilance database: Thrombosis at unusual sites. JThromb Haemost. 2021;00:1-5.

Background: Real-world experience with adenoviral vector vaccines against COVID-19 raised some safety concerns. Cases of cerebral vein thrombosis (CVT) associated with thrombocytopenia have been observed after the first dose of the adenoviral vector vaccines CHADOX1 NCOV-19 and Ad26.COV2.S.
Objectives: To assess the reporting rate of CVT as adverse drug reaction (ADR) for the COVID-19 vaccines authorised in Europe.
Methods: This observational study assessed the CVT reporting rate attributed to 4COVID-19 vaccines authorized in Europe, namely Tozinameran (Pfizer-Biontech),CX-024414(Moderna), CHADOX1 NCOV-19 (AstraZeneca), and Ad26.COV2.S (Janssen). Data on thrombotic ADRs reported on EudraVigilance database between 01 January 2021 and 30 July 2021, were collected. ADRs referring to CVT were identified. The reporting rate of CVT was expressed per 1 million person vaccinated-days with 95% confidence interval. Finally, an observed-to-expected (O/E) analysis was performed.
Results: The reporting rate of CVT per 1 million person vaccinated-days was 1.92 (95% confidence interval [CI], 1.71–2.12) for Tozinameran, 5.63 (95% CI, 4.74–6.64) for CX-024414, 21.60 (95% CI, 20.16–23.11) for CHADOX1 NCOV-19, and 11.48 (95% CI, 9.57–13.67) for Ad26.COV2.S. CVT occurred alongside thrombocytopenia for the 4 vaccines. The O/E ratio was greater than 1 for all 4vaccines, both with the lowest and the highest CVT background incidence.
Conclusions: This report on EudraVigilance data strengthens anecdotal findings on CVT following COVID-19 vaccinations. Although the EMA released an alert only for CHADOX1 NCOV-19 and Ad26.COV2.S, Tozinameran and CX-024414 also are complicated by CVT, albeit to lesser extent.

MAH Comments: The authors focus on CVT in the present report. The Warnings and Precautions Section of the CCDS includes language regarding, "severe cases of venous thrombosis at unusual sites such as cerebral venous sinus thrombosis, splanchnic vein thrombosis, as well as arterial thrombosis concomitant with thrombocytopenia and can lead to a fatal outcome." Regarding a potential comparison of the presented data to a background rate, the authors state, "the reporting rate of CVT could not be directly compared to the incidence rate in the general population, these being different measures that use different definitions of the time at risk. Therefore, whether the incidence of CVT is higher in vaccinated people than in the general population is beyond the scope of this study". Regarding potential comparisons of presented data between vaccines, the authors state, "The incidence of CVT for each vaccine could not be estimated lacking information on the extent of underreporting and exact time of occurrence. Only a minority of data are missing for sex and age group, but other strong thrombotic risk factors are not available (e.g., oral contraceptive use, thrombophilia abnormalities). Therefore, no causal inference should be done from these data due to missing information on possible confounders". While the authors' work adds to the growing body of information on CVT both with and without thrombocytopenia for the 4 vaccines presented, no new safety information was identified from this article.

Rapporteur assessment comment: Thromboembolism in subjects vaccinated with Janssen Covid-19 vaccine was further evaluated in EMEA/H/C/005737/MEA/032. Venous thromboembolism is included as a warning in section 4.4 and as an adverse reaction with frequency rare in section 4.8 in the SmPC. No new safety concern is detected here.

Blumberg D, Sridhar A, Lakshminrusimha S, Higgins RD, Saade G. COVID-19 vaccine considerations during pregnancy and lactation. Am J Perinatol.2021.

No abstract available.

MAH Comments: According to the authors, "Ad26.COV2.S is modified so that it cannot replicate. Therefore, there will be no viremia during pregnancy, and the vaccine is not expected to infect the fetus" and "Ad26.COV2.S is not likely to

enter breastmilk as viremia does not occur following administration." The authors concluded that "In the context of potential increased severity of COVID-19 during pregnancy and significant community transmission, immunization should be prioritized for pregnant women" and "To address the uncertainty, we applaud the creation of a COVID-19 vaccine pregnancy exposure registry". Use during pregnancy and lactation are considered missing information in the core RMP for Ad26.COV2.S.

Rapporteur assessment comment: No abstract has been presented. According to the MAH the authors suggest immunization for pregnant women. The SmPC section 4.6 describes limited experience but does not advise against use in pregnant women. No new information or knowledge regarding vaccination with Janssen Covid-19 vaccine during pregnancy has been provided in this paper. No new safety concern is detected here.

Chiang TP-Y, Connolly CM, Ruddy JA, et al. Antibody response to the Janssen/Johnson & Johnson SARS-CoV-2 vaccine in patients with rheumatic and musculoskeletal diseases. Ann Rheum Dis.2021.

No abstract available.

MAH Comments: The authors "compared the percentage of participants with detectable anti-RBD antibody in the J&J group (n=45) to the mRNA group (n=994) using Fisher's exact test [...] and "compared anti-RBD titres of the J&J group to those of the mRNA group using Wilcoxon rank-sum test. At a median (interquartile range) of 29 days (28-32) after vaccination, anti-RBD antibody was detectable in 36 participants who received the J&J vaccine compared with 906 who completed the mRNA vaccine series (80% vs 92%, p=0.03). Those who received J&J vaccination had a higher odds of negative antibody response (OR: 2.57, 95% CI 1.20 to 5.52, p=0.01) compared with those who completed the mRNA series. This association remained statistically significant in the adjusted logistic regression model (aOR: 3.86, 95% CI 1.37 to 10.84 p=0.01). Consistent with prior findings, use of rituximab, mycophenolate and glucocorticoids had a statistically significant association with negative antibody response [...] Median anti-RBD antibody titres in the J&J group were lower than the mRNA group (9.7 vs 250 U/mL; p<0.001)". The Warnings and Precautions Section of the CCDS states, "Immunocompromised persons including individuals receiving immunosuppressant therapy, may have a diminished immune response to TRADENAME". Please refer to Section 16.3.5.3, Use in Immunocompromised Patients for information regarding the topic of lack of efficacy/effect. Regarding clinical implications in the present study, the authors acknowledge that "no cut-off titre has been defined to associate with protection", and that "we did not analyse peri-vaccination immunosuppression dosing or timing". No new safety information was identified from this article.

Rapporteur assessment comment: According to the MAH description this report concern antibody levels after vaccination with either mRNA vaccine or Janssen covid-19 vaccine in subjects with rheumatic and musculoskeletal disease, where those who received the Janssen vaccine had a higher odds of a negative antibody test afterwards compared to those who were administered with mRNA vaccines. No new safety concern is detected here.

Choi, PYI. Thrombotic Thrombocytopenia after ChAdOx1 nCoV-19 vaccination. N Engl J Med. 2021.

No abstract available.

MAH Comments: In correspondence regarding a recent publication by (Greinacher 2021), the author states, "The manufacturers of Ad26.COV2.S [...] did not include that these vaccines use the same excipient, polysorbate 80, which is not present in other SARS-CoV-2 vaccines. Polysorbate 80 is a commonly used nonionic surfactant and drug stabilizer that is known to efficiently home to brain endothelial cells and cross the blood–brain barrier when complexed with nanoparticles", to which (Greinacher 2021) replied, "it seems unlikely that polysorbate 80 would still be present 1 or more weeks after vaccination when vaccine-induced immune thrombocytopenia (VITT) occurs". No plausible mechanism for polysorbate 80 was provided in this correspondence; reference was made to complexing with nanoparticles to cross the blood brain barrier (not applicable). Note is likewise made that polysorbate 80 is ubiquitous

and "at least 70% of injectable biological agents and monoclonal antibody treatments contain a polysorbate, most typically polysorbate 80 (Banerji 2020). No new safety information was identified from this article.

Rapporteur assessment comment: No abstract has been presented. According to the MAH this article concerns the excipient polysorbate 80. No new safety concern is detected here.

Garcia P, Anand S, Han J, et al. COVID19 vaccine type and humoral immune response in patients receiving dialysis. MedRxiv.

Background: Patients on dialysis vaccinated with the attenuated adenovirus SARS-CoV-2 vaccine might mount an impaired response to vaccination.
Methods: We evaluated the humoral vaccination response among 2,099 fully vaccinated patients receiving dialysis. We used commercially available assays (Siemens) to assess prevalence of no response or diminished response to COVID-19 vaccination by vaccine type. We defined "no seroconversion" as lack of change from negative to positive in total Receptor Binding Domain (RBD) Ig antibody, no detectable response on semiquantitative RBD IgG antibody (index value <1) as "no RBD IgG response", and a semiquantitative RBD IgG index value <10 as "diminished RBD IgG response"
Results: Of the 2,099 fully vaccinated patients on dialysis, the proportion receiving the mRNA1273, BNT162b2, and Ad26.COV2.S were 62% (n=1316), 20% (n=416) and 18% (n=367), respectively. A third (33.3%) of patients receiving the attenuated adenovirus Ad26.COV2.S vaccine failed to seroconvert and an additional 36% had no detectable or diminished IgG response even 28 to 60 days post-vaccination.
Conclusion: One in 3 fully vaccinated patients receiving dialysis had evidence of an impaired immune response to the attenuated adenovirus Ad26.COV2.S vaccine.

MAH Comments: The Warnings and Precautions Section of the CCDS states, "Immunocompromised persons including individuals receiving immunosuppressant therapy, may have a diminished immune response to TRADENAME". Please refer to Section 16.3.5.3, Use in Immunocompromised Patients for information regarding the topic of lack of efficacy/effect. Regarding limitations, the authors state, "Although a detectable serum antibody response is often equated with immunity, this relationship is not absolute. We were unable to test for cellular immunity or the presence of memory B cells". No new safety information was identified from this article.

Rapporteur assessment comment: This article describes three subjects receiving dialysis, who had an impaired immune response to the Janssen covid-19 vaccine. An impaired immune response can be expected from subjects receiving immunosuppressant treatment. No new safety concern is detected here.

Hause AM, Gee J, Johnson T, et al. Anxiety-related adverse event clusters after Janssen COVID-19 vaccination - Five U.S. Mass Vaccination Sites, April 2021. MMWR Morb Mortal Wkly Rep. 2021.

Abstract: Anxiety-Related Adverse Event Clusters After Janssen COVID-19 Vaccination- 5 U.S. Mass Vaccination Sites, April 2021. On 07 April 2021, after 5 weeks' use of the Janssen COVID-19 vaccine under FDA EUA, CDC received reports of clusters of anxiety-related events after administration of Janssen COVID-19 vaccine from 5 mass vaccination sites, all in different states. To further investigate these cases, CDC interviewed vaccination site staff members to gather additional information about the reported events and vaccination site practices. Four of the 5 sites temporarily closed while an investigation took place. Overall, 64 anxiety-related events, including 17 reports of syncope (fainting), an anxiety-related event, among 8,624 Janssen COVID-19 vaccine recipients, were reported from these sites for vaccines administered during 07 to 09 April. As a follow-up to these interviews, CDC analysed reports of syncope shortly after receipt of Janssen COVID-19 vaccine to the Vaccine Adverse Event Reporting System (VAERS), the vaccine safety monitoring program managed by CDC and FDA. To compare the occurrence of these events with those reported after receipt of other vaccines, reports of syncopal events after influenza vaccine administered in the 2019 to 2020 influenza season were also reviewed. Syncope after Janssen COVID-19 vaccination was reported to VAERS (8.2 episodes per 100,000 doses). By comparison, after influenza vaccination, the reporting rate of syncope was 0.05 episodes per 100,000 doses. Anxiety-related events can occur after any vaccination. It is important that vaccination providers are aware that anxiety-related AEs might be reported more frequently after receipt of the Janssen COVID-19 vaccine than after influenza vaccination and observe all COVID-19 vaccine recipients for any adverse reactions for at least 15minutes after vaccine administration.

MAH Comments: Regarding potential limitations, the authors state that, "the Janssen COVID-19 vaccine was not directly compared with other currently available COVID-19 vaccines", and that "because the Janssen COVID-19vaccine is administered as a single dose, this vaccine might be a more attractive option for persons who have needle aversion. Therefore, it is possible that some persons seeking Janssen COVID-19vaccination could be more highly predisposed to anxiety-related events after being vaccinated", and" in mass vaccination situations, an anxiety-related event witnessed by others on-site or reported through media coverage might provoke additional anxiety-induced episodes"

Rapporteur assessment comment: This paper describes anxiety-related adverse events associated with administration of Janssen covid-19 vaccine. A warning regarding anxiety-related reactions is already included in section 4.4 of the SmPC. No new safety concern is detected here.

Kuter DJ. Exacerbation of immune thrombocytopenia following COVID-19 vaccination. Br JHaematol. 2021.

Abstract: There is concern that COVID-19 vaccination may adversely affect immune thrombocytopenia (ITP) patients. Fifty-two consecutive chronic ITP patients were prospectively followed after COVID-19 vaccination. Fifteen percent had no worsening of clinical symptoms but no post-vaccination platelet count; 73% had no new symptoms and no significant platelet count decline. However, 12% had a median platelet count drop of 96% within 2 to 5 days post-vaccination with new bleeding symptoms; after rescue therapy with corticosteroids +/− intravenous immunoglobulin (IVIG), platelets recovered to >30 × 109/l a median three days later. ITP exacerbation occurred independently of remission status, concurrent ITP treatment, or vaccine type. Safety of a second vaccine dose needs careful assessment.

MAH Comments: Of the 52 patients with pre-existing chronic ITP, 4 were administered Ad26.COV2.S, 1 of whom experienced an ITP exacerbation. Overall, the authors state, "These results suggest that some patients with ITP might have a transient exacerbation of their thrombocytopenia, some with symptoms, within one week of their COVID-19 vaccination. Thrombocytopenia, in general, was responsive to IVIG and corticosteroids and it remains our recommendation that ITP patients should still undergo at least the initial vaccination for COVID-19". Additional information can be found in Section 16.3.2.3, Immune Thrombocytopenia.

Rapporteur assessment comment: Immune thrombocytopenia is included as a warning in section 4.4 of the SmPC and as an adverse reaction with unknown frequency in section 4.8. No new safety concern is detected here.

Lim J, Han M, Kim Y, et al. New-onset nephrotic syndrome after Janssen COVID-19 vaccination: a case report and literature review. J Korean Med Sci. 2021;36(30):e218.

Abstract: Various COVID-19 vaccines are being developed, which show practical preventive effects. Here, we report a 51-year-old healthy man with nephrotic syndrome secondary to minimal change disease (MCD) after Ad26.COV.2 (Janssen) vaccination. He had no comorbid disease and received Ad26.COV.2 on 13 April 2021. Seven days after vaccination, he developed edema and foamy urine. Edema rapidly aggravated with decreased urine volume. He was admitted to the hospital 28 days after vaccination, and his body weight increased by 21 kg after vaccination. His serum creatinine level was 1.54 mg/dL, and 24-h urinary protein excretion was 8.6 g/day. Kidney biopsy revealed no abnormality in the glomeruli and interstitium of the cortex and medulla under the light microscope. Electron microscopy revealed diffuse effacement of the podocyte foot processes, thus, he was diagnosed with MCD. High-dose steroid therapy was applied, and his kidney function improved 3 days after steroid therapy. Three weeks after steroid use, his serum creatinine decreased to 0.95 mg/dL, and spot urine protein-to-creatine decreased to 0.2 g/g. This case highlights the risk of new-onset nephrotic syndrome secondary to MCD after vectored COVID-19 vaccination. Although the pathogenesis is uncertain, clinicians need to be careful about adverse renal effects of COVID-19 vaccines.

MAH Comments: The presentation, clinical course, and outcome for the patient, a 51-year-old-male who experienced nephrotic syndrome after Ad26.COV2.S vaccine is presented in the 01 July 2021 to 31 July 2021 Monthly Summary Safety Report (MSSR) (adverse event report [AER] 4.1(b)), including any received follow-up. Regarding the pathogenesis for MCD, the authors acknowledged that, "Although the exact pathogenesis is still unelucidated, podocyte injury by circulating factors released by T cells is considered the main mechanism". Additionally, the authors provided a summary table for 11 cases of new-onset and relapsing MCD vaccination with either the mRNA or AstraZeneca Ad26.COV2.S vaccines. There were 5 new onset (3 male, 2 female; age 51 to 80s, all after mRNA Ad26.COV2.S vaccine) and 6 relapses (4 male, 2 female; age 22 to 60s, 4 mRNA and 2 AstraZeneca Ad26.COV2.S vaccine). Authors stated, "All cases of MCD occurred within 10 days after vaccination with the first dose and the histopathological findings showed typical MCD findings" and "vaccination-related nephrotic syndrome secondary to MCD was reported in other vaccines, such as influenza, hepatitis B, pneumococcus, and measles." A cumulative evaluation of the cases did not provide sufficient evidence to establish a causal relationship between Ad26.COV2.S and MCD/Nephrotic syndrome. The Company will continue to monitor these events through routine pharmacovigilance.

Rapporteur assessment comment: Nephrotic syndrome and MCD has been further evaluated in the MSSRs. No new safety concern is detected here.

Lospinoso K, Nichols CS, Malachowsk SJ, et al. A case of severe cutaneous adverse reaction following administration of the Janssen Ad26.COV2.S COVID-19 Vaccine. JAAD Case Rep.

2021;13:134-137.

No abstract available.

MAH Comments: The authors described a case in a 74-years-old patient with panhypopituitarism secondary to craniopharyngioma resection, vision loss of the left eye, neurogenic bladder, and obstructive sleep apnea who presented 3 days after vaccination with Ad26.COV2.S with severe cutaneous adverse reaction (SCAR). The differential diagnosis included acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS), and AGEP-DRESS overlap. The patient was known to be allergic to sulfa drugs and amoxicillin-clavulanic acid and no prior vaccination related reactions were reported. He denied recent illness or medication changes prior to onset. At an unspecified date (unknown temporal relationship to vaccination) the patient took prednisone 5 mg daily for adrenal insufficiency, but his community dermatologist increased this to 20 mg daily for a suspected stasis dermatitis flare when this eruption was mostly on his lower extremities. Physical examination revealed a generalized distribution (50% of the body surface area) of erythematous plaques, studded with numerous small, non-follicular pustules. The rash spared the face, genitals, and mucosae. Significant acral swelling was observed in the absence of palpable lymphadenopathy. Laboratory test results at presentation (day 13 after vaccination) were notable for an elevated white blood cell count reflecting absolute neutrophilia and an elevated eosinophil count. Within 24 hours, his eosinophil count roughly tripled to 1.6 x 109 cells/L. Hepatic function panel results were within the normal limits, and creatinine levels elevated transiently but returned to normal. A biopsy from the right shoulder revealed epidermal spongiosis with focal, occasional, subcorneal neutrophilic pustules and dermal neutrophilic inflammation with eosinophils, consistent with a spongiotic and pustular drug eruption. A direct immunofluorescence study from the same site was negative. The electrocardiogram was within normal limits. Patient responded to oral prednisone 20 mg orally daily and topical steroids. At follow-up (day 20 after vaccination), his liver enzymes and creatinine level remained stable and within the normal limits, his absolute eosinophil count was also within the normal range, and his skin had improved. The acral swelling was also reduced. The authors concluded that this SCAR case presented a temporal association with Ad26.COV2.S vaccination with no comments on the causal role of the vaccine. Of note, no skin patch test was performed to exclude the causality of other not reported concomitant drugs knowing that the patient had underlying panhypopituitarism including adrenal insufficiency. Therefore, there is insufficient evidence of the causal role of the vaccine in the development of SCAR.

Rapporteur assessment comment: No abstract was presented on this case-report describing a 74-year-old male who experienced SCAR three days after vaccination. In the MSSR EMEA/H/C/005737/MEA/014.4 a cumulative review through 31July2021 including case narratives of severe cutaneous adverse reactions (SCAR), including AGEP and DRESS was presented by the MAH. No new safety concern is detected here.

Nassar M, Nso N, Gonzalez C, et al. COVID-19 vaccine-induced myocarditis: Case report with literature review. Diabetes Metab Syndrome: Clin Res Reviews. 2021;15(5):102205.

No abstract available.

MAH Comments: In the initial version of the article, the authors stated, "We tracked eighteen cases of myocarditis concerning the Janssen vaccine in the medical literature (Table 3)"; however, upon review, the remaining 17 cases were associated with mRNA vaccines (AER: 4.1(b) The authors have since corrected this error within the online publication. Please refer to Section 16.2.1.1.2, Myocarditis and Pericarditis for further discussion of this topic.

Rapporteur assessment comment: No abstract has been presented. The case report concerns myocarditis, which is a topic that has been further investigated (see section of myocarditis, pericarditis). No new safety concern is detected here.

Pozdnyakova V, Botwin GJ, Sobhani K, et al. Decreased Antibody Responses to Ad26.COV2.S Relative to SARS-CoV-2 mRNA Vaccines in Patients with Inflammatory Bowel Disease. Gastroenterol. 2021.

No abstract available.

MAH Comments: The Warnings and Precautions Section of the CCDS states, "Immunocompromised persons including individuals receiving immunosuppressant therapy, may have a diminished immune response to TRADENAME". Please

refer to Section 16.3.5.3, Use In Immunocompromised Patients for information regarding the topic of lack of efficacy/effect. The authors of the present article indicated that, "recipients of [Janssen] had significantly lower antibody levels than recipients of mRNA platform vaccines, independent of immune-modifying therapies (IMT) use", however "[t]he clinical implications of qualitatively positive but quantitatively lower antibody levels among Ad26.CoV2.S recipients are unknown. In a study of 20 Ad26.COV2.S recipients from the COV1001 phase I-IIa clinical trial, neutralizing antibody responses were significantly lower against the B.1.351 and P.1 variants than the original sWA1/2020 strain, but T cell responses and functional non-neutralizing antibody responses were largely preserved [...] These findings underscore the fact that antibody titers represent only one component of the immune response". No new safety information was identified from this article.

Rapporteur assessment comment: No abstract has been presented on this report describing significantly lower antibody titers in subjects that received Janssen covid-19 vaccine compared to those that received mRNA vaccines, independent of which immune-modifying therapy that was used. No new safety is concern detected here.

Rosner CM, Genovese L, Tehrani BN, et al. Myocarditis Temporally Associated with COVID-19 Vaccination. Circulation. 2021.

No abstract available.

MAH Comments: Of the 7 patients hospitalised for acute myocarditis like illness following COVID-19 vaccination from 2 US medical centers, 1 patient (a 28-year-old white male; AER: 4.1(b) received Ad26.COV2.S. All patients were males less than 40 years of age; irrespective of vaccine received, "Hospital length of stay was 3±1 days and all patients' symptoms resolved by hospital discharge." According to the authors, "Additional study is needed to confirm if the rate of myocarditis-like illness is higher after vaccination than the background rate of myocarditis among similar aged individuals in the population", which the authors note "is diagnosed in approximately 10-20 individuals per 100,000/year". Please refer to Section 16.2.1.1.2, Myocarditis and Pericarditis for further discussion of this topic

Rapporteur assessment comment: No abstract has been presented. The report concerns myocarditis, which is a topic that has been further investigated (see section of myocarditis, pericarditis). No new safety concern is detected here.

Class Effect Literature

Douxfils J, Favresse J, Dogné J-M, et al. Hypotheses behind the very rare cases of thrombosis with thrombocytopenia syndrome after SARS-CoV-2 vaccination. Thromb Res. 2021;203:163-171.

Abstract: As of 04 April 2021, a total of 169 cases of cerebral venous sinus thrombosis (CVST) and 53 cases of splanchnic vein thrombosis were reported to EudraVigilance among around 34 million people vaccinated in the European Economic Area (EEA) and UK with COVID-19 Vaccine AstraZeneca, a chimpanzee adenoviral vector (ChAdOx1) encoding the spike protein antigen of the SARS-CoV-2 virus. The first report of the European Medicines Agency gathering data on 20 million people vaccinated with Vaxzevria® in the UK and the EEA concluded that the number of post-vaccination cases with thromboembolic events as a whole reported to EudraVigilance in relation to the number of people vaccinated was lower than the estimated rate of such events in the general population. However, the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) concluded that unusual thromboses with low blood platelets should be listed as very rare side effects of Vaxzevria®, pointing to a possible link. The same issue was identified with the COVID-19 Vaccine Janssen (Ad26.COV2.S). Currently, there is still a sharp contrast between the clinical or experimental data reported in the literature on COVID-19 and the scarcity of data on the unusual thrombotic events observed after the vaccination with these vaccines. Different hypotheses might support these observations and should trigger further in vitro and ex vivo investigations. Specialised studies were needed to fully understand the potential relationship between vaccination and possible risk factors in order to implement risk minimisation strategies.

MAH Comments: Within the various hypotheses for thrombosis with thrombocytopenia syndrome (TTS) summarised by the authors, note is made of their recommendation that "Intravenous administration of COVID-19 vaccine cannot be excluded and should be part of pharmacokinetic investigations"; however no connection between such administration and current knowledge of TTS regarding demographic characteristics (female sex, specific age groups) or specific vascular beds (e.g., splanchnic, dural/cerebral sinuses) was provided. Incorrect route of administration is monitored.

Rapporteur assessment comment: TTS is included as a warning in section 4.4 of the SmPC and as a very rare adverse reaction in section 4.8. No new safety concern is detected here.

Gessler F, Schmitz AK, Dubinski D, et al. Neurosurgical considerations regarding decompressive craniectomy for intracerebral hemorrhage after SARS-CoV-2-vaccination in vaccine induced thrombotic thrombocytopenia-VITT. J Clin Med. 2021;10(13).
Abstract: Given the ongoing global SARS-CoV-2-vaccination efforts, clinical awareness needs to be raised regarding the possibility of an increased incidence of SARS-CoV-2-vaccine-related immune-mediated thrombocytopenia in patients with intracerebral hemorrhage (ICH) secondary to cerebral sinus and vein thrombosis (CVT) requiring (emergency) neurosurgical treatment in the context of vaccine-induced immune thrombotic thrombocytopenia (VITT). Only recently, an association of vaccinations and cerebral sinus and vein thrombosis has been described. In a number of cases, neurosurgical treatment is warranted for these patients and special considerations are warranted when addressing the perioperative coagulation. We, herein, describe the past management of patients with VITT and established a literature-guided algorithm for the treatment of patients when addressing the impaired coagulation in these patients. Increasing insights addressing the pathophysiology of SARS-CoV-2-vaccine-related immune-mediated thrombocytopenia guide physicians in developing an interdisciplinary algorithm taking into account the special considerations of this disease.

MAH Comments: In addition to the case presentation reporting administration of the Janssen vaccine, the authors propose a general treatment algorithm for cerebral venous thrombosis; however, acknowledging that, "Surgical treatment of ICH related to venous stasis resulting from CVT remains challenging. To address such a challenging clinical situation, a rapid multidisciplinary approach that combines the expertise of a multitude of specialists including experts in hematology, immunology radiology, critical care, and neurosurgery is ultimately warranted". As such, no specific changes to the current reference safety information are warranted at this time. Additional information can be found in Section 16.3.1.2, Thrombosis with Thrombocytopenia Syndrome.

Rapporteur assessment comment: TTS is included as a warning in section 4.4 of the SmPC and as a very rare adverse reaction in section 4.8. No new safety concern is detected here.

Greinacher A, Selleng K, Mayerle J, et al. Anti-platelet factor 4 antibodies causing VITT do not cross-react with SARS-CoV-2 Spike Protein. Blood. 2021.
Abstract: VITT is a severe AE of ChAdOx1 nCoV-19 COVID-19 vaccine (Vaxzevria) and COVID-19 vaccine Janssen (Ad26.COV2.S), and associated with unusual thrombosis. VITT is caused by anti-platelet factor 4(PF4) antibodies activating platelets through their FcγRIIa receptors. Antibodies activating platelets through FcγRIIa receptors have also been identified in COVID-19 patients. These findings raise concern that vaccination-induced antibodies against anti-SARS-CoV-2 spike protein cause thrombosis by cross-reacting with PF4. Immunogenic epitopes of PF4 and SARS-CoV-2 spike protein were compared using in-silico prediction tools and 3D-modelling. The SARS-CoV-2 spike protein and PF4share at least one similar epitope. Reactivity of purified anti-PF4 antibodies from patients with VITT was tested against recombinant SARS-CoV-2 spike protein. However, none of the affinity purified anti-PF4 antibodies from 14 VITT patients cross-reacted with SARS-CoV-2 spike protein. Sera from 222 polymerase chain reaction (PCR) confirmed COVID--19 patients from 5 European centres were tested by PF4/heparin ELISA and PF4-dependent platelet activation assays. We found anti- PF4 antibodies in 19 of 222 (8.6%) COVID-19 patient sera. However, only 4 showed weak to moderate platelet activation in the presence of PF4, and none of these patients developed thrombotic complications. Among 10 of 222 (4.5%) COVID-19 patients with thrombosis, none showed PF4-dependent platelet activating antibodies. In conclusion, antibodies against PF4 induced by vaccination do not cross-react with the SARS-CoV-2 spike protein, indicating that the intended vaccine-induced immune response against SARS-CoV-2 spike protein is not the trigger of VITT. PF4-reactive antibodies found in COVID-19 patients of the present study were not associated with thrombotic complications.

MAH Comments: The present work by Greinacher et al. adds to the body of knowledge on potential mechanisms of Thrombosis with Thrombocytopenia Syndrome (TTS). Note however is made of the potential for mutations in the spike protein sequence utilised that may alter immunogenicity (Harvey 2021). Data from the cohort of patients with COVID-19 illness presented in the article's table 1 indicates that, whether with or without thrombotic events, approximately 8 to 10% of the cohort demonstrated some positivity to PF4/heparin ELISA assays and that none demonstrated heparin dependent platelet activation by ELISA. The clinical significance of these findings, either separately or in combination, remains to be determined.

Rapporteur assessment comment: The article presents data from one study suggesting that antibodies against PF4 induced by vaccination do not cross-react with the SARS-CoV-2 spike protein. The clinical relevance of these findings has not been determined. No new safety information is detected here.

Marchandot B, Carmona A, Trimaille A, Curtiaud A, Morel O. Procoagulant microparticles: a possible link between vaccine-induced immune thrombocytopenia (VITT) and cerebral sinus venous thrombosis. J

Thromb Thrombolysis. 2021.
Abstract: The objective of this study was to define the relative contributions of 3 major pro and anti-coagulation pathways (heparin-antithrombin, protein C, and tissue factor (TF)) in the thrombogenic responses that occur in large and small vessels of the brain. Cerebral venous sinus thrombosis was induced by topical application of FeCl3 on the superior sagittal sinus, while photoactivation of fluorescein was used to induce thrombus formation in cerebral microvessels. Heparin, activated protein C (APC), and antibodies to either APC or TF were used to assess thrombogenesis in wild-type mice. Mutant mice that overexpress the endothelial protein C receptor (EPCR-tg) or with TF deficiency in Tie2-expressing endothelial cells (LTFE) were also used. Thrombus formation in the superior sagittal sinus of wild-type mice was attenuated by heparin and in EPCR-tg mice, while treatment with the APC antibodies enhanced thrombogenesis. Arteriolar thrombosis was largely unresponsive to the interventions studied. However, in cerebral venules, thrombosis was inhibited by heparin and in EPCR-tg mice. TF antibody treatment also inhibited venular thrombosis, with a similar attenuation noted in LTFE mice. Thrombin promotes while the APC pathway blunts thrombus formation in an experimental model of cerebral venous sinus thrombosis. TF involvement is more evident in cerebral microvascular thrombogenesis, with endothelial cell-associated TF mediating this response in venules, but not arterioles.

MAH Comments: In addition to a review of previously described mechanisms involving anti-PF4antibodies, the authors focus on "Microparticles (MPs) refer to small vesicles, ranging from 0.1 to 2 μm, originating from the plasma membrane of stimulated or apoptotic cells including, platelets, leukocytes and endothelial cells", specifically "Procoagulant MPs (platelet and monocyte-derived) are circulating MPs that express phosphatidylserine (PS) and tissue factor (TF) and contribute to pro-coagulant responses." While the authors state that, "Altogether, this results in enhanced PS and TF expression and subsequent thrombin generation more likely to occur in the cerebral venous system due to its specific thrombogenesis process", the latter statement regarding specificity for cerebral venous circulation versus. non-cerebral venous circulation is left unexplained by the work cited (Nagai 2010). No new safety information was identified from this article.

Rapporteur assessment comment: This paper focus on additional possible mechanisms besides of anti-PF4 antibodies in the development of TTS and CSVT. TTS is included as a warning in section 4.4 of the SmPC and as a very rare adverse reaction in section 4.8. Venous thromboembolism is included as a warning in section 4.4 and as an adverse reaction with frequency rare in section 4.8 in the SmPC. No new safety concern is detected here.

Mastellos DC, Skendros P, Lambris JD. Is complement the culprit behind COVID-19 vaccine-related adverse reactions? J Clin Invest. 2021;131(11):e151092.
No abstract available.
MAH Comments: The authors hypothesize that, "the observed thrombotic complications may partly reflect immune complex–triggered complement activation through the classical pathway" as a downstream effect of anti–platelet factor 4 (PF-4) immune complex recognition by C1q (a soluble pattern recognition molecule of the classical pathway that binds to the Fc portion of IgG molecules), and point to the use of complement C5 inhibitor eculizumab in 2 cases (Tiede 2021) non-Janssen vaccine case report; (Muir 2021). However, a note is made that both patients had been anticoagulated, with one also receiving intravenous immunoglobulin (IVIG), information presented in this article regarding the classical complement pathway remains hypothesis generating at this time.

Rapporteur assessment comment: No abstract has been presented. According to the MAH this paper discusses the involvement of antibody-mediated platelet activation in the development of TTS. TTS is included as a warning in section 4.4 of the SmPC and as a very rare adverse reaction in section 4.8. No new safety concern is detected here.

Nguyen H, Chen L-Y, Khan N, et al. SARS-CoV-2 Spike Protein-Induced Platelet Activation: Mechanism for Virus and Vaccine-Induced Thrombotic Thrombocytopenia. In Review; 2021.
Abstract: COVID-19 pandemic stimulated an extremely fast development of effective vaccines. Recent studies found platelet-activating antibodies against platelet factor 4 (PF4) in both clinically ill COVID-19 patients and VITT patients. Here, we use various tools to identify the binding reaction of the SARS-CoV-2 spike glycoprotein (SP) with PF4that results in immunogenic platelet-activating PF4/SP complexes. This binding is evidenced by an increase in mass, optical intensity, and stable binding force observed by quartz crystal microbalance, enzyme immune assay, and force spectroscopy, respectively. The SP induced an increase in the size of PF4 and switched the surface zeta potential of the PF4 from positive to negative values as evaluated by dynamic light scattering. The SP-induced platelet aggregation was identified by functional assay and flow cytometry but in a concentration-dependent manner. Our results indicated that the formed PF4/SP complexes can, on one hand, trigger the formation of PF4-antibodies and on the other hand mediate/activate platelets followed by inducing thrombotic events, which is the mechanism for excessive procoagulant

activity observed in COVID-19 patients. With vector-based vaccines, we suggest that soluble SP are produced during the transcription process, forming antigenic PF4/SP complexes that result in a high rate of clotting effects in vaccinated individuals with Ad26.COV2.S and ChAdOx1nCoV-19 vaccines. An additional consideration of PF4/SP complexes in the current guidelines for the diagnosis of VITT will improve the treatment in patients. Our results serve a high demand to develop an effective method to treat COVID-19 patients and improve the safety for COVID-19 vaccination.

MAH Comments: The authors state the following, "As PF4/SP complexes also induce platelet aggregation, we suggest an additional consideration to the guidance [...] If serum is negative in the screening test for HIT antibodies but positive in HIPA/SRA, the critical PF4:SP concentration ratio that forms platelet-activating PF4/SP complexes is reached. In this case, heparin or even high-dose heparin treatment is possible". The authors' statement is considered hypothesis-generating at this time, and current recommendations (Bussel 2021) regarding avoidance of heparin use in suspected TTS remain prudent. The Warnings and Precautions section of the CCDS state, "In individuals with suspected thrombosis with thrombocytopenia following administration of TRADENAME, the use of heparin may be harmful and alternative treatments may be needed. Healthcare professionals should consult applicable guidance [...] and/or consult specialists (e.g., hematologists) to diagnose and treat this condition." No changes to this language are warranted at this time.

Rapporteur assessment comment: This study aimed to further investigate possible mechanisms for virus and vaccine induced thrombotic thrombocytopenia. TTS is included as a warning in section 4.4 of the SmPC and as a very rare adverse reaction in section 4.8. No new safety concern is detected here.

Sánchez van Kammen M, Heldner MR, Brodard J, et al. Frequency of Thrombocytopenia and Platelet Factor 4/Heparin Antibodies in Patients With Cerebral Venous Sinus Thrombosis Prior to the COVID-19 Pandemic. JAMA. 2021;326(4):332-338.

Abstract: Cases of cerebral venous sinus thrombosis in combination with thrombocytopenia have recently been reported within 4 to 28 days of vaccination with the ChAdOx1 nCov-19 (AstraZeneca/Oxford) and Ad.26.COV2.S (Janssen/Johnson & Johnson) COVID-19 vaccines. An immune-mediated response associated with platelet factor 4/heparin antibodies has been proposed as the underlying mechanism.

Objective: To determine the frequencies of admission thrombocytopenia, heparin-induced thrombocytopenia, and presence of platelet factor 4/heparin antibodies in patients diagnosed with cerebral venous sinus thrombosis prior to the COVID-19 pandemic.

Design,/Setting/Participants: This was a descriptive analysis of a retrospective sample of consecutive patients diagnosed with cerebral venous sinus thrombosis between January 1987 and March 2018 from 7 hospitals participating in the International Cerebral Venous Sinus Thrombosis Consortium from Finland, the Netherlands, Switzerland, Sweden, Mexico, Iran, and Costa Rica. Of 952 patients, 865with available baseline platelet count were included. In a subset of 93 patients, frozen plasma samples collected during a previous study between September 2009 and February 2016 were analysed for the presence of platelet factor 4/heparin antibodies.

Exposures: Diagnosis of cerebral venous sinus thrombosis.

Outcomes/Measures: Frequencies of admission thrombocytopenia (platelet count<150 ×103/μL), heparin-induced thrombocytopenia (as diagnosed by the treating physician), and platelet factor 4/heparin IgG antibodies (optical density >0.4, in a subset of patients with previously collected plasma samples). Results: Of 865 patients (median age, 40 years [interquartile range, 29 to 53 years], 70% women), 73 (8.4%; 95% CI, 6.8% to 10.5%) had thrombocytopenia, which was mild (100 to 149 ×103/μL) in 52 (6.0%), moderate (50 to 99 ×103/μL) in 17 (2.0%), and severe (<50 ×103/μL) in 4(0.5%). Heparin-induced thrombocytopenia with platelet factor 4/heparin antibodies was diagnosed in a single patient (0.1%; 95% CI, <0.1% to 0.7%). Of the convenience sample of 93 patients with cerebral venous sinus thrombosis included in the laboratory analysis, 8 (9%) had thrombocytopenia, and none (95% CI, 0% to 4%) had platelet factor 4/heparin antibodies.

Conclusions: In patients with cerebral venous sinus thrombosis prior to the COVID-19 pandemic, baseline thrombocytopenia was uncommon, and heparin-induced thrombocytopenia and platelet factor 4/heparin antibodies were rare. These findings may inform investigations of the possible association between the ChAdOx1 nCoV-19 and Ad26.COV2.S COVID-19 vaccines and cerebral venous sinus thrombosis with thrombocytopenia.

MAH Comments: While the present analysis does not allow for frequency calculations, it suggests that pre-pandemic patients with both CVST and thrombocytopenia (defined here as <100 ×103/μL) presented at a median age in their forties, were evenly divided between male and female sex, and approximately two-thirds had 1 or more identifiable etiologies for their thrombocytopenia. The convenience sample of sera from 93 patients (8 of whom had baseline thrombocytopenia) suggests that PF4/heparin antibodies would be infrequently detected in an undifferentiated population with CVST, however conclusions cannot be confidently drawn. In conjunction with background incidence rate data from (ACCESS 2021a), such descriptive studies may be a useful adjunct in understanding risk factors and prevention strategies for CVST; however, no new safety information was identified from this article.

Rapporteur assessment comment: In this paper the frequencies of admission thrombocytopenia, heparin-induced thrombocytopenia, and presence of platelet factor 4/heparin antibodies in patients diagnosed with cerebral venous sinus thrombosis prior to the COVID-19 pandemic were evaluated. TTS is included

as a warning in section 4.4 of the SmPC and as a very rare adverse reaction in section 4.8. No new safety concern is detected here.

Thiele T, Ulm L, Holtfreter S, et al. Frequency of positive anti-PF4/polyanion antibody tests after COVID-19 vaccination with ChAdOx1 nCoV-19 and BNT162b2. Blood. 2021.

Abstract: Vaccination using the adenoviral vector COVID-19 vaccine ChAdOx1 nCoV-19 (AstraZeneca) has been associated with rare vaccine-induced immune thrombotic thrombocytopenia (VITT). Affected patients test strongly positive in PF4/polyanion enzyme immunoassays (EIAs) and serum-induced platelet activation is maximal in the presence of PF4. We determined the frequency of anti-PF4/polyanion antibodies in healthy vaccinees and assessed whether PF4/polyanion EIA-positive sera exhibit platelet-activating properties after vaccination with ChAdOx1 nCoV-19 (n=138) or BNT162b2 (BioNTech/Pfizer; n=143). In total, 19 of 281 participants tested positive for anti-PF4/polyanion antibodies post-vaccination (All: 6.8% [95%CI, 4.4-10.3]; BNT162b2: 5.6% [95%CI, 2.9-10.7]; ChAdOx1 nCoV-19: 8.0% [95%CI, 4.5-13.7%]). Optical densities were mostly low (between 0.5 to 1.0 units; reference range, <0.50) and none of the PF4/polyanion EIA-positive samples induced platelet activation in the presence of PF4. We conclude that positive PF4/polyanion EIAs can occur after SARS-CoV-2 vaccination with both mRNA- and adenoviral vector-based vaccines, but the majority of these antibodies likely have minor (if any) clinical relevance. Accordingly, low-titre positive PF4/polyanion EIA results should be interpreted with caution when screening asymptomatic individuals after vaccination against COVID-19. Pathogenic platelet-activating antibodies that cause VITT do not occur commonly following vaccination.

MAH Comments: The detection of anti-PF4 antibodies in healthy post-vaccination patients who were administered either mRNA or Ad26 vector vaccines, along with evidence that, "Naturally occurring antibodies that react with PF4 bound to heparin are present in 3 to 8 percent of the general population without HIT", (Coutre 2021), indicate that the significance of a positive PF4 antibody immunoassay of low optical density versus clinical presentation, diagnosis, and treatment remains indeterminate at this time. Overlapping confidence intervals between the AstraZeneca and Pfizer vaccines preclude interpretation of a difference in frequency between the studied groups.

Rapporteur assessment comment: This study has investigated the frequency of positive anti-PF4 polyanion antibody tests after administration of the covid-19 adenoviral vector vaccine ChAdOx1 nCoV-19 and the covid-19 mRNA vaccine BNT162b2. TTS is included as a warning in section 4.4 of the SmPC and as a very rare adverse reaction in section 4.8. No new safety concern is detected here.

1.3.6. Lack of efficacy in controlled clinical trials

During the reporting period, no information relevant to lack of efficacy from controlled clinical trials was received for Ad26.COV2.S.

1.3.7. Late-breaking information

In line with the pharmacovigilance local regulation in Mexico, on 26 Aug 2021, a communication was submitted to the local Health Authority (specifically to the Pharmacovigilance National Center) to inform them about the Significant Safety Issues (SSI) of Capillary Leak Syndrome (CLS), Guillain-Barré Syndrome (GBS), TTS along with the actions that will be taken regarding these SSIs.

On 30 Aug 2021, the Food and Drug Administration concurred with the updates to the EUA Fact Sheets that were submitted on 28 July 2021 and 27 Aug 2021. The Healthcare Providers Administering Vaccine includes updates to the warnings and precautions Module 5.4 Syncope and Overall safety summary post-authorisation experience and Module 6.2. for Lymphadenopathy, Syncope, Paresthesia, Hypoesthesia, Tinnitus, Diarrhoea, and Vomiting. In addition, the EUA Fact Sheet for Recipients and Caregivers has been updated to reflect the changes made to the Healthcare Providers Factsheet.

Multisystem Inflammatory Syndrome

On 2 Sept 2021, a Signal of multisystem inflammatory syndrome (MIS) for COVID-19 vaccines (EPITT ref. No. 19732) was confirmed by the PRAC for all Covid-19 vaccines approved in the EU.

Menstrual Disorders
On 02 Sept 2021, in the final assessment report (EMEA/H/C005737/MEA 014.4) corresponding to the 5th MSSR for JNJ-784367735 (Ad26.COV2.S), dated 15 Aug 2021, the PRAC requested the MAH to provide a cumulative review of cases reporting a menstrual disorder or post-menopausal haemorrhage following vaccination. PSUSA.

Rapporteur assessment comment:

The signal on MIS and the evaluation of menstrual disorders have been handled within other procedure and are not commented further in this current PSUSA Assessment.

2. Signal and risk evaluation

2.1. Summary of safety concerns

At the beginning of the reporting period
The summary of safety concerns (i.e., important identified risks, important potential risks, and missing information) at the beginning of the reporting period are summarised in Table 38 and are based on RMP version 1.0; dated 18 February 2021.

Table 38: Important Identified Risks, Important Potential Risks and Missing Information at the Beginning of the Reporting Period

Important Identified Risks	None
Important Potential Risks	Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD)
Missing Information	Use during pregnancy Use in breastfeeding women Use in immunocompromised patients Use in patients with autoimmune or inflammatory disorders Use in frail patients with comorbidities (eg, chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders) Interaction with other vaccines Long-term safety

At the end of the reporting period
The summary of safety concerns at the end of the reporting period are summarised in Table 39; RMP version 3; date 11 Aug 2021.

Table 39: Important Identified Risks, Important Potential Risks and Missing Information at the End of the Reporting Period

Important Identified Risks	Anaphylaxis Thrombosis with Thrombocytopenia Syndrome Guillain-Barré Syndrome
Important Potential Risks	Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) Venous thromboembolism Immune thrombocytopenia Capillary Leak Syndrome

Missing Information	Use during pregnancy Use in breastfeeding women Use in immunocompromised patients Use in patients with autoimmune or inflammatory disorders Use in frail patients with comorbidities (eg, chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders) Interaction with other vaccines Long-term safety

Rapporteur assessment comment: These RMP updates are in line with procedural steps taken and scientific information during reporting period.

2.2. Signal evaluation

- Tabular overview of signals: new, ongoing or closed during the reporting interval 25-Feb-2021 to 24-Aug-2021.

Signal Term	Date Detected DD/MMM/YYYY	Status (Ongoing or Closed)	Date Closed (for Closed Signals) DD/MMM/YYYY	Source of Signal	Reason for Evaluation and Summary of Key Data	Method of Signal Evaluation	Action(s) Taken or Planned
Hypotension	12/Mar/2021	NEW SIGNAL; CLOSED/ SAFETY ISSUE NOT CONFIRMED	12/Mar/2021	Health Authority	On 12MAR2021 a signal was identified for the event of hypotension with the use of COVID-19 vaccine based on a request from the United States Food and Drug Administration for a search of the Janssen global safety database for reports of hypotension associated with Janssen COVID-19 vaccine Lot #1805022 following receipt of reports for this topic. This signal was created because it is a safety topic with regulatory interest.	The evaluation method included a cumulative case series review of available data in the Global Safety Database through 12MAR2021 (n=1 Spontaneous case) reporting the following Medical Dictionary for Regulatory Activities Preferred Term: Hypotension.	Routine Pharmacovigilance Activities.
Thromboembolic Events (TBE) with thrombocytopenia	04/Apr/2021	NEW SIGNAL; CLOSED/ SAFETY ISSUE CONFIRMED	19/May/2021	Health Authority	On 04APR2021 a signal was identified for Thromboembolic Events (TBE) with thrombocytopenia with the use of COVID-19 VACCINE AD26.COV2.S based on European Medicines Agency	The evaluation method included a cumulative case series review of available data in the Global Safety Database through 07MAY2021. A Total of 52 Thrombosis with Thrombocytopeni	Update to the United States Pharmacovigilance Plan. Update to Risk Management Plan. Direct Health Care Professional Communication. Additional monitoring of

					(EMA) Pharmacovigilance Risk Assessment Committee (PRAC) request. This signal was created because it is a safety topic with regulatory interest.	a Syndrome (TTS) cases reviewed from post-marketing reporting and 17 TTS cases from clinical trials (no TTS cases reported from Sisonke COV3012). The search strategy for spontaneous and Sisonke trial: TTS was retrieved with the following search: Concomitant Standardized MedDRA Query (SMQ) Embolic and thrombotic events, AND High-Level Term (HLT) Thrombocytopenias OR SMQ Haematopoietic cytopenias. The search strategy for clinical trials: SMQ: Embolic and thrombotic events, SMQ: Haemorrhages (as a proxy for	study participants. Change in study protocol. Informed Consent Form update. Company Core Data Sheet update. Change to local labeling/package insert. Investigator's Brochure update. Update patient information. Health Authority Communication. Letter to Investigators. Targeted follow-up questionnaire. Vaccination pause in United States and hold in the clinical trials between 13-Apr-2021 and 23-Apr-2021.; Risk Management Plan (RMP) Update. Important Identified Risk (Thrombosis with thrombocytopenia syndrome), Pharmacovigilanc

Signal Term	Date Detected DD/MMM/YYYY	Status (Ongoing or Closed)	Date Closed (for Closed Signals) DD/MMM/YYYY	Source of Signal	Reason for Evaluation and Summary of Key Data	Method of Signal Evaluation	Action(s) Taken or Planned
						potential thrombocytopenia), SMQ: Haematopoietic cytopenias or HLT Thrombocytopenias. Analysis of relevant clinical trial data was performed. The Food and Drug Administration Vaccine Adverse Event Reporting System data are included in the post-marketing search strategy.	e Plan. Risk Minimizations Measures. New Study/Registry: Clinical trial, Preclinical study (incudes Toxicology, Pharmacokinetic/ pharmacodynamic, etc.), Case control study anti PF4 test and Platelets activation and other invitro studies.
Diarrhoea	22/Apr/2021	NEW SIGNAL; CLOSED/ SAFETY ISSUE CONFIRMED	16/Jun/2021	Internal Signal Detection - Company Database - Aggregate	On 22APR2021 a signal was identified for the event Diarrhoea, with the use of COVID-19 Vaccine Ad26.COV2.S based on a statistical signal of disproportionate reporting identified within the Company Global Safety Database.; This signal was created based on the statistical association between the drug and the event.	The evaluation method included a cumulative case series review of available data in the Global Safety Database through 24MAY2021 (n=437 cases) reporting the Preferred Terms from the Medical Dictionary for Regulatory Activities Standardised MedDRA Query:	Routine Pharmacovigilance Activities; Company Core Data Sheet update

						Noninfectious diarrhoea (broad). A calculation of the postmarketing reporting frequency was performed.	
Dizziness	22/Apr/2021	NEW SIGNAL; CLOSED/ SAFETY ISSUE CONFIRMED	21/Jun/2021	Internal Signal Detection - Company Database - Aggregate, Internal Signal Detection - Food and Drug Administration Vaccine Adverse Event Reporting System.	On 22APR2021 a signal was identified for Dizziness with the use of COVID-19 VACCINE AD26.COV2.S based on disproportionality that has been observed for Dizziness in the Company database and Vaccine Adverse Event Reporting System. This signal was created based on the statistical association between the drug and the event.	This signal was evaluated in the context of anxiety -related reactions. The global safety database was searched for all cases reporting Ad26.COV2.S as suspect, or suspect-interacting vaccine, received from post-marketing sources cumulatively through 31 May 2021, and reported adverse events coded to the Medical Dictionary for Regulatory Activities (MedDRA; version 24.0) Preferred Terms (PTs) of: Acute stress disorder,	Company Core Data Sheet update. Routine Pharmacovigilance Activities

Signal Term	Date Detected DD/MMM/YYYY	Status (Ongoing or Closed)	Date Closed (for Closed Signals) DD/MMM/YYYY	Source of Signal	Reason for Evaluation and Summary of Key Data	Method of Signal Evaluation	Action(s) Taken or Planned
						Agitation, Aichmophobia, Algophobia, Anxiety disorder, Aphonia psychogenic, Blood pressure decreased, Colitis psychogenic, Device psychogenic complication, Dizziness , Dysphonia psychogenic, Nausea, Neurogenic bowel, Neurological complication associated with device, Neurological procedural complication, Neuropsychiatric symptoms, Neuropsychiatric syndrome, Neurosis, Panic attack, Panic disorder, Panic reaction, Pharmacophobia, Polydipsia psychogenic, Post	

						procedural complication, Post procedural constipation, Post procedural diarrhoea, Post procedural discomfort, Post-traumatic stress disorder, Procedural complication, Procedural dizziness, Procedural hypotension, Procedural nausea, Procedural pain, Procedural vomiting, Psychogenic blindness, Psychogenic dysuria, Psychogenic erectile dysfunction, Psychogenic movement disorder, Psychogenic pseudosyncope, Psychogenic respiratory distress,	

Signal Term	Date Detected DD/MMM/YYYY	Status (Ongoing or Closed)	Date Closed (for Closed Signals) DD/MMM/YYYY	Source of Signal	Reason for Evaluation and Summary of Key Data	Method of Signal Evaluation	Action(s) Taken or Planned
						Psychogenic seizure, Psychogenic tremor, Psychogenic visual disorder, Respiratory tract procedural complication, Seizure, Skin procedural complication, Torticollis psychogenic, Vomiting. This cumulative search of the global safety database through 31 May 2021 retrieved a total of 3,529 post-marketing cases meeting the above-mentioned search criteria. All cases of Dizziness retrieved from this global database search were assessed.	
Loss of consciousness	22/Apr/2021	NEW SIGNAL; CLOSED/ SAFETY ISSUE CONFIRMED	21/Jun/2021	Internal Signal Detection - Company Database -	On 22APR2021 a signal was identified for Loss of consciousness with the use of COVID-19	This signal was evaluated in the context of anxiety -related reactions. The global safety	Company Core Data Sheet update.; Routine Pharmacovigilanc e Activities.

				Aggregate, Internal Signal Detection - Food and Drug Administration Vaccine Adverse Event Reporting System	VACCINE AD26.COV2.S based on disproportionality that has been observed for multiple events related to Loss of consciousness in the Company database and/or Vaccine Adverse Event Reporting System.; This signal was created due to the association with serious medical consequences, based on the impact of this event in a new population, due to the significant case volume, based on the statistical association between the drug and the event, and based on the temporal association of the events. Including Loss of consciousness in labeling could decrease post-vaccination driving, and prevent some motor vehicle accidents as a result.	database was searched for all cases reporting Ad26.COV2.S as suspect, or suspect-interacting vaccine, received from post-marketing sources cumulatively through 31 May 2021, and reported adverse events coded to the Medical Dictionary for Regulatory Activities (MedDRA; version 24.0) Preferred Terms (PTs) of: Acute stress disorder, Agitation, Aichmophobia, Algophobia, Anxiety disorder, Aphonia psychogenic, Blood pressure decreased, Colitis psychogenic, Device psychogenic complication,	

Signal Term	Date Detected DD/MMM/YYYY	Status (Ongoing or Closed)	Date Closed (for Closed Signals) DD/MMM/YYYY	Source of Signal	Reason for Evaluation and Summary of Key Data	Method of Signal Evaluation	Action(s) Taken or Planned
						Dizziness , Dysphonia psychogenic, Nausea, Neurogenic bowel, Neurological complication associated with device, Neurological procedural complication, Neuropsychiatric symptoms, Neuropsychiatric syndrome, Neurosis, Panic attack, Panic disorder, Panic reaction, Pharmacophobia, Polydipsia psychogenic, Post procedural complication, Post procedural constipation, Post procedural diarrhoea, Post procedural discomfort, Post-traumatic stress disorder, Procedural complication,	

						Procedural dizziness, Procedural hypotension, Procedural nausea, Procedural pain, Procedural vomiting, Psychogenic blindness, Psychogenic dysuria, Psychogenic erectile dysfunction, Psychogenic movement disorder, Psychogenic pseudosyncope, Psychogenic respiratory distress, Psychogenic seizure, Psychogenic tremor, Psychogenic visual disorder, Respiratory tract procedural complication, Seizure, Skin procedural complication,	

Signal Term	Date Detected DD/MMM/YYYY	Status (Ongoing or Closed)	Date Closed (for Closed Signals) DD/MMM/YYYY	Source of Signal	Reason for Evaluation and Summary of Key Data	Method of Signal Evaluation	Action(s) Taken or Planned
						Torticollis psychogenic, Vomiting. This cumulative search of the global safety database through 31 May 2021 retrieved a total of 3,529 post-marketing cases meeting the above-mentioned search criteria. All cases retrieved from this global database search reporting loss of consciousness were assessed.	
Lymphadenopathy	22/Apr/2021	NEW SIGNAL; CLOSED/ SAFETY ISSUE CONFIRMED	21/Jun/2021	Internal Signal Detection - Company Database – Aggregate	On 22APR2021 a signal was identified for the event Lymphadenopathy, with the use of COVID-19 VACCINE AD26.COV2.S based on a statistical signal of disproportionate reporting identified within the Company Global Safety Database. This signal was created based on the statistical	The evaluation method included a cumulative case series review of available data in the Global Safety Database through 17MAY2021 (n=99 cases; 98 post-marketing, 1 non-Company non-interventional study) reporting the following Medical	Company Core Data Sheet update; Routine Pharmacovigilance Activities

					association between the drug and the event.	Dictionary for Regulatory Activities Preferred Terms: Lymphadenopathy, Injection site lymphadenopathy, Administration site lymphadenopathy, Lymph node abscess, Lymph node pain, Lymphadenitis, Lymphoedema, and Vaccination site lymphadenopathy. A review of relevant scientific literature and post-marketing reporting frequency were performed.	
Tinnitus	22/Apr/2021	NEW SIGNAL; CLOSED/ SAFETY ISSUE CONFIRMED	08/Jul/2021	Internal Signal Detection - Company Database - Aggregate, Internal Signal Detection - Food and Drug	On 22APR2021 a signal was identified for the event Tinnitus, with the use of COVID-19 VACCINE AD26.COV2.S based on a statistical signal of disproportionate reporting identified within the Company	The evaluation method included a cumulative case series review of available data in the Global Safety Database through 19MAY2021 (n=135 cases; Spontaneous post-marketing cases)	Company Core Data Sheet update. Investigator's Brochure update.; Routine Pharmacovigilance Activities and inclusion in the Periodic Benefit Risk Evaluation

Signal Term	Date Detected DD/MMM/YYYY	Status (Ongoing or Closed)	Date Closed (for Closed Signals) DD/MMM/YYYY	Source of Signal	Reason for Evaluation and Summary of Key Data	Method of Signal Evaluation	Action(s) Taken or Planned
				Administration Vaccine Adverse Event Reporting System.	Global Safety Database and the Vaccine Adverse Event Reporting System database. This signal was created based on the statistical association between the drug and the event.	reporting Preferred Terms from the Medical Dictionary for Regulatory Activities (MedDRA) Standardized MedDRA Query: Hearing impairment. Analysis of relevant clinical trial data and relevant scientific literature was performed. A calculation of reporting rates of the events was performed.	Report. Monitoring in the Monthly Safety Summary Report.
Cutaneous Sensory Changes	22/Apr/2021	NEW SIGNAL; CLOSED/ SAFETY ISSUE CONFIRMED	29/Jun/2021	Internal Signal Detection - Company Database - Aggregate, Internal Signal Detection - Food and Drug Administration Vaccine Adverse	On 22APR2021 a signal was identified for Cutaneous Sensory Changes with the use of COVID-19 VACCINE AD26.COV2.S based on disproportionality that has been observed for multiple events related to Cutaneous Sensory Changes in the Company database and/or Vaccine Adverse Event	The evaluation method included a cumulative case series review of available data in the Global Safety Database through 17MAY2021 (n=565 cases; 164 serious, 401 nonserious) reporting the following Medical Dictionary for	Company Core Data Sheet update; Routine Pharmacovigilance Activities

Signal Term	Date Detected DD/MMM/YYYY	Status (Ongoing or Closed)	Date Closed (for Closed Signals) DD/MMM/YYYY	Source of Signal	Reason for Evaluation and Summary of Key Data	Method of Signal Evaluation	Action(s) Taken or Planned
				Event Reporting System.	Reporting System. This signal was created based on the statistical association between the drug and the event.	Regulatory Activities Preferred Terms: Paraesthesia, Hypoaesthesia, Dysaesthesia, Pain of skin and Sensitive skin.	
Vomiting	22/Apr/2021	NEW SIGNAL; CLOSED/ SAFETY ISSUE CONFIRMED	16/Jun/2021	Internal Signal Detection - Company Database - Aggregate	On 22APR2021 a signal was identified for the event Vomiting, with the use of COVID-19 VACCINE AD26.COV2.S based on a statistical signal of disproportionate reporting identified within the Company Global Safety Database.; This signal was created based on the statistical association between the drug and the event.	The evaluation method included a cumulative case series review of available data in the Global Safety Database through 24MAY2021 (n=475 post-marketing cases) reporting the following Medical Dictionary for Regulatory Activities Preferred Terms: Vomiting, Vomiting projectile, and Vomiting psychogenic.	Company Core Data Sheet update; Routine Pharmacovigilance Activities
Anxiety-related Reactions	22/Apr/2021	NEW SIGNAL; CLOSED/ SAFETY ISSUE CONFIRMED	21/Jun/2021	Aggregate report preparation (eg PBRER), Internal	On 22APR2021 a signal was identified for Anxiety-related Reactions with the use of COVID-19 VACCINE	The evaluation method included a cumulative case series review of available data in the Global Safety	Company Core Data Sheet update; Routine Pharmacovigilance Activities

Signal Term	Date Detected DD/MMM/YYYY	Status (Ongoing or Closed)	Date Closed (for Closed Signals) DD/MMM/YYYY	Source of Signal	Reason for Evaluation and Summary of Key Data	Method of Signal Evaluation	Action(s) Taken or Planned
				Signal Detection - Company Database - Aggregate; Preparation of the Monthly Safety Summary Report for Covid-19 Vaccine	AD26.COV2.S during preparation of the Monthly Safety Summary Report for Covid-19 Vaccine and based on disproportionate reporting of related Preferred Terms identified within the Company Global Safety Database.; This signal was created due to a drug class effect (vaccine) and based on the temporal association of the events.	Database through 31MAY2021 (n=3529 post-marketing cases) reporting the following Medical Dictionary for Regulatory Activities Preferred Terms: Acute stress disorder, Agitation, Aichmophobia, Algophobia, Anxiety disorder, Aphonia psychogenic, Blood pressure decreased, Colitis psychogenic, Device psychogenic complication, Dizziness , Dysphonia psychogenic, Nausea, Neurogenic bowel, Neurological complication associated with device, Neurological	

Signal Term	Date Detected DD/MMM/YYYY	Status (Ongoing or Closed)	Date Closed (for Closed Signals) DD/MMM/YYYY	Source of Signal	Reason for Evaluation and Summary of Key Data	Method of Signal Evaluation	Action(s) Taken or Planned
						procedural complication, Neuropsychiatric symptoms, Neuropsychiatric syndrome, Neurosis, Panic attack, Panic disorder, Panic reaction, Pharmacophobia, Polydipsia psychogenic, Post procedural complication, Post procedural constipation, Post procedural diarrhoea, Post procedural discomfort, Post-traumatic stress disorder, Procedural complication, Procedural dizziness, Procedural hypotension, Procedural nausea, Procedural pain, Procedural vomiting, Psychogenic blindness,	

Signal Term	Date Detected DD/MMM/YYYY	Status (Ongoing or Closed)	Date Closed (for Closed Signals) DD/MMM/YYYY	Source of Signal	Reason for Evaluation and Summary of Key Data	Method of Signal Evaluation	Action(s) Taken or Planned
						Psychogenic dysuria, Psychogenic erectile dysfunction, Psychogenic movement disorder, Psychogenic pseudosyncope, Psychogenic respiratory distress, Psychogenic seizure, Psychogenic tremor, Psychogenic visual disorder, Respiratory tract procedural complication, Seizure, Skin procedural complication, Torticollis psychogenic, Vomiting.	
Guillain-Barré syndrome	05/May/2021	NEW SIGNAL; CLOSED/ SAFETY ISSUE NOT CONFIRMED	28/May/2021	Internal Signal Detection - Company Database - Aggregate	On 05MAY2021 a signal was identified for the event Guillain-Barre syndrome, with the use of COVID-19 VACCINE AD26.COV2.S based on a statistical signal	The evaluation method included a cumulative case series review of available data in the Global Safety Database through 19MAY2021	Routine Pharmacovigilance Activities and inclusion in the Periodic Benefit Risk Evaluation Report.

Signal Term	Date Detected DD/MMM/YYYY	Status (Ongoing or Closed)	Date Closed (for Closed Signals) DD/MMM/YYYY	Source of Signal	Reason for Evaluation and Summary of Key Data	Method of Signal Evaluation	Action(s) Taken or Planned
					of disproportionate reporting identified within the Company Global Safety Database. This signal was created due to the association of events with fatal outcomes/serious medical consequences and the percentage of serious cases.	(n=50 cases; n=46 Spontaneous and n=4 Clinical trial cases) reporting Preferred Terms from the Medical Dictionary for Regulatory Activities (MedDRA) Standardized MedDRA Query: Guillain-Barre Syndrome (Narrow). Analysis of relevant clinical trial data, review of relevant scientific literature, and review of review of Food and Drug Administration Vaccine Adverse Event Reporting System data that are included in the post-marketing search strategy was performed.	

Signal Term	Date Detected DD/MMM/YYYY	Status (Ongoing or Closed)	Date Closed (for Closed Signals) DD/MMM/YYYY	Source of Signal	Reason for Evaluation and Summary of Key Data	Method of Signal Evaluation	Action(s) Taken or Planned
Guillain-Barré syndrome	07/Jul/2021	NEW SIGNAL; CLOSED/ SAFETY ISSUE CONFIRMED	10/Aug/2021	Health Authority	This signal was previously reviewed by the Company in May 2021. A new request has been received that warrants a new review of this signal. On 07JUL2021 a new signal was identified for the event of Guillain-Barre syndrome with the use of the COVID-19 VACCINE AD26.COV2.S based on a request from the United States Food and Drug Administration Center for Biologics Evaluation and Research to update the United States Covid-19 Vaccine Fact Sheet for the COVID-19 VACCINE AD26.COV2.S. This signal was created because it is a safety topic with regulatory interest..	The evaluation method included a cumulative case series review of available data in the Global Safety Database through 30JUN2021 (n=108 cases; 104 Post-marketing cases and 4 clinical trial cases) reporting Preferred Terms from the Medical Dictionary for Regulatory Activities (MedDRA) Standardized MedDRA Query: Guillain-Barre syndrome (Narrow). A review of relevant scientific literature and analysis of observed/expected was performed.	Risk Management Plan update: Important Identified Risk. Company Core Data Sheet update. Change to local labeling/package insert. Investigator's Brochure update. Update to patient information.; Routine Pharmacovigilance Activities and inclusion in the Periodic Benefit Risk Evaluation Report.

Signal Term	Date Detected DD/MMM/YYYY	Status (Ongoing or Closed)	Date Closed (for Closed Signals) DD/MMM/YYYY	Source of Signal	Reason for Evaluation and Summary of Key Data	Method of Signal Evaluation	Action(s) Taken or Planned
Thrombocytopenia	01/Jun/2021	NEW SIGNAL; CLOSED/ SAFETY ISSUE NOT CONFIRMED	13/Jul/2021	Internal Signal Detection - Company Database - Aggregate, Internal Signal Detection - Food and Drug Administration Vaccine Adverse Event Reporting System	On 01JUN2021 a signal was identified for the event Platelet count decreased with the use of COVID-19 VACCINE AD26.COV2.S based on a statistical signal of disproportionate reporting identified within the Company Global Safety Database and the Food and Drug Administration Vaccine Adverse Event Reporting System.; This signal was created due to the association of the events with fatal outcomes/serious medical consequences and the fact that it is a safety topic with regulatory interest.	The evaluation method included a cumulative case series review of available data in the Global Safety Database through 18JUN2021 (n=264 cases; Spontaneous post-marketing cases (234) and clinical trial cases (30) reporting Preferred Terms from the Medical Dictionary for Regulatory Activities (MedDRA) High Level Term: Thrombocytopenias and Standardized MedDRA Query: Hematopoietic thrombocytopenias. Analysis of relevant clinical trial data was performed. A review of reports with terms described above from the AdVAC platform.	Risk Management Plan (RMP) Update: Important Potential Risk. Health Authority Communication. Monitoring in the Monthly Safety Summary Report.; Routing Pharmacovigilance Activities and inclusion in the Periodic Benefit Risk Evaluation Report.

Signal Term	Date Detected DD/MMM/YYYY	Status (Ongoing or Closed)	Date Closed (for Closed Signals) DD/MMM/YYYY	Source of Signal	Reason for Evaluation and Summary of Key Data	Method of Signal Evaluation	Action(s) Taken or Planned
Capillary Leak Syndrome	15/Jun/2021	NEW SIGNAL; CLOSED/ SAFETY ISSUE NOT CONFIRMED	25/Jun/2021	Internal Signal Detection - Company Database - Aggregate	On 15JUN2021 a signal was identified in the context of routine pharmacovigilance of the Global Company Safety Database for the event of Capillary Leak Syndrome with the use of COVID-19 VACCINE AD26.COV2.S based on the identification of 3 Post-Marketing/Solicited cases. This signal was created due to the association of the events with fatal outcomes/serious medical consequences and the fact that it is a safety topic with regulatory interest.	The evaluation method included a cumulative case series review of available data in the Global Safety Database through 18JUN2021 (n=3 cases; Post-marketing cases. Of the 3 cases, 2 fatal) reporting the following Medical Dictionary for Regulatory Activities Preferred Terms: Capillary leak syndrome and Capillary permeability increased. Analysis of relevant clinical trial data was performed (No cases of Capillary leak syndrome as of 18JUN2021). A review of relevant scientific literature was performed.	Risk Management Plan update: New Important Potential Risk, Risk Minimizations Measures, Assessment of Effectiveness of Risk Minimizations Measures. Direct Health Care Professional Communication. Change in study protocol. Company Core Data Sheet update. Change to local labeling/package insert. Investigator's Brochure update. Update patient information. Health Authority Communication. Letter to Investigators; Routine Pharmacovigilanc e Activities, inclusion in the Periodic Benefit

Signal Term	Date Detected DD/MMM/YYYY	Status (Ongoing or Closed)	Date Closed (for Closed Signals) DD/MMM/YYYY	Source of Signal	Reason for Evaluation and Summary of Key Data	Method of Signal Evaluation	Action(s) Taken or Planned
							Risk Evaluation Report, and monitoring in the Monthly Safety Summary Report.
Capillary Leak Syndrome	16/Sep/2021	NEW SIGNAL; CLOSED/ SAFETY ISSUE CONFIRMED	16/Sep/2021	Aggregate report preparation (eg PBRER)	This signal has been reviewed by the Company in the past. New information has been received that warrants a new review of this signal. On 16SEP2021 a signal was identified for the event of Capillary Leak Syndrome with the use of COVID-19 VACCINE AD26.COV2.S based on a review of additional post-marketing cases.; This signal was created due to the association of events with fatal outcomes/serious medical consequences, due to the fact that this is a preventable event, and due to a drug class effect.	The evaluation method included a cumulative case series review of available data in the Global Safety Database through 16SEP2021 (n=6 cases; Spontaneous case types) reporting the following Medical Dictionary for Regulatory Activities Preferred Term: Capillary Leak Syndrome. A drug-class labeling comparison was performed.	Risk Management Plan (RMP) Update: Capillary Leak Syndrome is removed from the list of Safety Concerns (Important Potential Risk) based on the very limited impact on Public Health due to the very rare nature of this Syndrome. Company Core Data Sheet update; Inclusion in Periodic Benefit Risk Evaluation Report.
Blindness	05/Jul/2021	NEW SIGNAL; CLOSED/ SAFETY ISSUE NOT CONFIRMED	23/Aug/2021	Health Authority	On 05JUL2021 a signal was identified for the event of Blindness with the use of Ad26.COV2.S	The evaluation method included a cumulative case series review of available data in	Routine Pharmacovigilanc e Activities and inclusion in the Periodic Benefit

Signal Term	Date Detected DD/MMM/YYYY	Status (Ongoing or Closed)	Date Closed (for Closed Signals) DD/MMM/YYYY	Source of Signal	Reason for Evaluation and Summary of Key Data	Method of Signal Evaluation	Action(s) Taken or Planned
					(Janssen COVID-19 Vaccine) based on a request from the Korean Ministry of Health to perform a review of the topic. This signal was created because it is a safety topic with regulatory interest.	the Global Safety Database through 31JUL2021 (n=225 cases; Spontaneous and Non-interventional cases) reporting Preferred Terms from the Medical Dictionary for Regulatory Activities (MedDRA) High Level Term: Visual impairment and blindness (excluding colour blindness). A review of relevant scientific literature and observed/expecte d analysis was performed.	Risk Evaluation Report.
Flare of Autoimmune disorders[a]	16/Jul/2021	NEW SIGNAL; ONGOING/ EVALUATION	----	Literature	On 16JUL2021 a signal was identified for the event of Flare of autoimmune disorders with the use of COVID-19 VACCINE AD26.COV2.S based on literature reports of newly diagnosed or	----	----

Signal Term	Date Detected DD/MMM/YYYY	Status (Ongoing or Closed)	Date Closed (for Closed Signals) DD/MMM/YYYY	Source of Signal	Reason for Evaluation and Summary of Key Data	Method of Signal Evaluation	Action(s) Taken or Planned
					flares of autoimmune diseases following vaccination with anti-SARS-CoV-2 mRNA (psoriasis, cutaneous lupus erythematosus, and IgG4 related nephritis) and Astra-Zeneca vaccines (minimal change disease). This signal was created due to biological plausibility and based on the temporal association of the events.		
Venous Thromboembolism[b]	21/Jul/2021	NEW SIGNAL; ONGOING/ EVALUATION	---	Internal Signal Detection Company Database - Aggregate	On 21JUL2021 a signal was identified for the event Venous thrombosis with the use of COVID-19 VACCINE AD26.COV2.S based on a statistical signal of disproportionate reporting identified within the Company Global Safety Database.; This signal was created due to the association of events with fatal outcomes/serious medical consequences, the potential of the event to alter the	---	---

Signal Term	Date Detected DD/MMM/YYYY	Status (Ongoing or Closed)	Date Closed (for Closed Signals) DD/MMM/YYYY	Source of Signal	Reason for Evaluation and Summary of Key Data	Method of Signal Evaluation	Action(s) Taken or Planned
					benefit-risk profile, due to the significant case volume, due to the appearance of similar findings in multiple data sources, and based on the temporal association of the events.		
Myocarditis and Pericarditis	19/Jul/2021	NEW SIGNAL; CLOSED/ SAFETY ISSUE NOT CONFIRMED	10/Aug/2021	Aggregate report preparation (eg PBRER), Other (describe below); Review of observed versus expected analysis for cardiac inflammatory disorders has noted a disproportionality in the United States, over time.	On 19JUL2021 a signal was identified for Myocarditis and Pericarditis with the use of COVID-19 VACCINE AD26.COV2.S based on an increased observed versus expected ratio in the United States, over time for cardiac inflammatory disorders. This signal was created due to a newly identified risk for mRNA COVID-19 vaccines, because this is an unlisted event, based on the statistical association between the drug and the event, and based on the temporal association of the events.	The evaluation method included a cumulative case series review of available data in the Global Safety Database through 21JUL2021 (n=79 cases; all case types) reporting Preferred Terms from the Medical Dictionary for Regulatory Activities (MedDRA) High Level Terms: Noninfectious myocarditis and Noninfectious pericarditis. In addition, a cumulative search of the Standardised Medical Regulatory	Routine Pharmacovigilance Activities.

Signal Term	Date Detected DD/MMM/YYYY	Status (Ongoing or Closed)	Date Closed (for Closed Signals) DD/MMM/YYYY	Source of Signal	Reason for Evaluation and Summary of Key Data	Method of Signal Evaluation	Action(s) Taken or Planned
						Dictionary for Regulatory Activities (SMQ) Cardiomyopathy (Broad) was conducted. Data mining analysis of the Food and Drug Administration Vaccine Adverse Event Reporting System, EudraVigilance, and World Health Organization VigiBase was performed. Analysis of relevant clinical and preclinical trial data was performed. Analysis of relevant data from observational databases was performed. A drug-class labeling comparison, calculation of reporting rates of the events, and a review of relevant scientific	

Signal Term	Date Detected DD/MMM/YYYY	Status (Ongoing or Closed)	Date Closed (for Closed Signals) DD/MMM/YYYY	Source of Signal	Reason for Evaluation and Summary of Key Data	Method of Signal Evaluation	Action(s) Taken or Planned
						literature was performed.	
Vasculitis[c]	06/Aug/2021	NEW SIGNAL; ONGOING/ EVALUATION	----	Internal Signal Detection - Company Database - Single case assessment, Internal Signal Detection - Food and Drug Administration Vaccine Adverse Event Reporting System.	On 06AUG2021 a signal was identified for Vasculitis with the use of COVID-19 VACCINE AD26.COV2.S based on receipt and review of an autopsy report for case 4.1(b) The autopsy report confirmed a latency of 11 days between the receipt of the Janssen COVID-19 vaccine and the first diagnosis of vasculitis, and it confirmed that vasculitis was among the causes of death for the patient. This signal was created due to the association of events with serious medical consequences, due to biological plausibility, based on the statistical association between the drug and the event, and based on the temporal association of the events.	----	----
Multisystem Inflammatory Syndrome[d]	03/Sep/2021	NEW SIGNAL; CLOSED/ SAFETY ISSUE NOT-CONFIRMED	23/Sep/2021	Health Authority	On 03SEP2021 a signal was identified for the event of Multisystem inflammatory syndrome with the use of COVID-19 VACCINE AD26.COV2.S based on a European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) request to perform a cumulative review of the topic.; This signal was created because it is a safety topic with regulatory interest.	The evaluation method included a cumulative case series review of available data in the Global Safety Database through 02SEP2021 (n=32 cases; 29 Spontaneous cases, 3 interventional clinical study (unblinded to placebo) cases; Of the 29 spontaneous cases, 18 were fatal) reporting Medical Dictionary for Regulatory Activities Preferred Terms recommended by the European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC). Data mining analysis of the Food and Drug Administration	Routine Pharmacovigilance Activities and inclusion in the Periodic Benefit Risk Evaluation Report.

Signal Term	Date Detected DD/MMM/YYYY	Status (Ongoing or Closed)	Date Closed (for Closed Signals) DD/MMM/YYYY	Source of Signal	Reason for Evaluation and Summary of Key Data	Method of Signal Evaluation	Action(s) Taken or Planned
						Vaccine Adverse Event Reporting System, EudraVigilance, and World Health Organization VigiBase was performed. A calculation of reporting rates of the events was performed. A review of relevant scientific literature was performed.	
Transverse Myelitis-Encephalitis (including Acute Disseminated Encephalomyelitis)[e]	23/Sep/2021	NEW SIGNAL; ONGOING/ EVALUATION	---	Health Authority; August 2021 Monthly Safety Summary Report preliminary assessment report.	On 23SEP2021 a signal was identified for Transverse Myelitis- Encephalitis (including Acute disseminated Encephalomyelitis) with the use of COVID-19 VACCINE AD26.COV2.S based on AUG21-Monthly Safety Summary Report preliminary assessment report.; This signal was created because it is a	---	---
					safety topic with regulatory interest.		

Key: #=Number; COVID-19=Coronavirus Disease of 2019; EMA=European Medicines Agency; HLT=High-level Term; MedDRA=Medical Dictionary for Regulatory Activities; mRNA=Messenger Ribonucleic Acid; n=Number of Cases; PBRER=Periodic Benefit Risk Evaluation Report; PF4=Platelet Factor 4; PRAC=Pharmacovigilance Risk Assessment Committee; PT=Preferred Term; RMP=Risk Management Plan; SARS-CoV-2=Severe Acute Respiratory Coronavirus 2; SMQ=Standardised MedDRA Query; TBE=Thromboembolic Events; TTS=Thrombocytopenia Syndrome.

a: A signal evaluation was completed and a report is attached with this PBRER. The report contains additional details on the evaluation results (see Appendix 7.5., Autoimmune Disorders). The signal is being closed and at this time, the status of ongoing is only procedural.

b: The evaluation of VTE was concluded during the preparation of this report. Additional details can be found in Section 14., Late-Breaking Information.

c: A signal evaluation was completed and a report is attached with this PBRER. The report contains additional details on the evaluation results (see Appendix 7.15., Vasculitis). The signal is being closed and at this time, the status of ongoing is only procedural.

d: Additional information on the evaluation completed can be found in Appendix 7.1 Multisystem Inflammatory Syndrome.

e: A signal evaluation was completed and a report is attached with this PBRER. The report contains additional details on the evaluation results (see Appendix 7.16., Transverse Myelitis and Encephalitis including ADEM). The signal is being closed and at this time, the status of ongoing is only procedural.

2.2.1. Closed Signals

2.2.1.1. Closed and Refuted Signals

During the reporting period, the following signals were closed and considered refuted by the Company.

Blindness

Request: On 25 June 2021, the Company received the following request from the Korean Health Authority: "Submit the evaluation data on relatedness to the drug and Observed/Expected ratio of blindness cases from designated medical events. Submit explanation materials on reporting period and

calculation of cumulative case counts."

Rapporteur assessment comment:

An in-depth analysis of blindness has been presented with the MSSR **MEA 14.4.** no safety concern has been detected these analyses and in additional interval cases presented with MSSR MEA 14.5, 6 and 14.7. The MAH continues presenting cases of blindness in the upcoming MSSRs.

Myocarditis and Pericarditis

A review of the broad and restricted observed versus expected (O/E) analysis for cardiac inflammatory disorders in the June COVID-19 MSSR found a disproportionality in the 18 to 59-year-old age group in US with a sustained statistically significant increase identified in the broad O/E analysis through 21 July 2021. A cumulative review was conducted and included in the August MSSR.

Rapporteur assessment comment:

Myocarditis and pericarditis have been assessed in depth, based on cumulative reviews included in the MSSRs; the last one in the August MSSR, which had a later DLP than the current PSUSA. These data are therefore not further addressed in this current AR.

Nevertheless, pericarditis and myocarditis should be closely monitored for the coming SSRs and PSURs.

Flare of Autoimmune Disorders

Introduction

A safety concern of *use in patients with autoimmune or inflammatory disorders* is included as missing information in the RMP.

On 16 July 2021, the MAH identified a signal for flare of autoimmune disorders based on literature reports, and a preliminary analysis of available information. The MAH has provided a cumulative review based on preclinical and clinical data, post-marketing safety data, as well as a literature search, regarding whether there may be a causal association between flare of autoimmune disorders and vaccination with Ad26.COV2.S; covering the time period from 25 February to 24 August 2021.

Epidemiology of Autoimmune Diseases in General Population

Autoimmune diseases represent a heterogeneous group of over 80 inflammatory disorders with an aberrant immune response against autoantigens (Theoflopoulos 2017).

The majority of autoimmune diseases disproportionately affect women (Gleicher 2007; see Table 1). The prevalence of autoimmune conditions ranges from less than 5 per 100,000 to more than 500 per 100,000. According to the MAH the estimated total (summed across diseases) incidence (90 per 100,000 person-years) and prevalence (3%) are conservative estimates since there are no data available for some diseases and some conditions (that is psoriasis, antiphospholipid syndrome) are not included. The table below summarizes incidence, prevalence, and sex distribution of autoimmune diseases (Cooper 2003). The MAH also states that because of increasing prevalence of individual autoimmune conditions over the past few decades, coincidence of events in the context of vaccination should be expected (Wraith 2003).

Table 1: Incidence, Prevalence, and Sex Distribution of Autoimmune Diseases

Disease	Incidence per 100,000 Person-Years	Prevalence per 100,000	Percent Female (%)
Addison's disease	0.6	14.0	93
Chronic active hepatitis	0.7	0.4	88
Glomerulonephritis			
Primary	3.6	40.0	32
IgA	2.4	23.2	67
Diabetes (Type 1)			
Age <20 years	12.2	192.0	48
Age 20 years and up[a]	8.1	No data	35
Graves' disease/hyperthyroidism			
All ages	13.9	1151.5	88
Ages 10 to 19	No data	106.9	67
Multiple sclerosis	3.2	58.3	64
Myasthenia gravis	0.4	5.1	73
Myocarditis			
All ages	0.1	No data	45
Ages <15	4.1	No data	44
Pernicious anemia	No data	150.9	67
Polymyositis/dermatomyositis	1.8	5.1	67
Primary biliary cirrhosis	0.9	3.5	89
Rheumatoid arthritis			
Juvenile (age <16)	17	148	68
Adult	23.7	860.0	75
Systemic sclerosis (scleroderma)	1.4	4.4	92
Sjogren disease	3.9[b]	14.4	94

Table 1 continued:

Disease	Incidence per 100,000 Person-Years	Prevalence per 100,000	Percent Female (%)
Systemic lupus erythematosus	7.3	23.8	88
Thyroiditis/hypothyroidism			
Ages >19	21.8	791.7	95
Ages 10 to 19	No data	532.1	83
Uveitis	18.9	1.7	50
Vitiligo	No data	400.2	52
Wegener's granulomatosis	1.0	3.0	51
Primary systemic vasculitis	2.0	14.5	43
Total	90	3225	80

Key: IgA=Immunoglobulin A.
Adapted from: Cooper GS, Stroehla BC. The epidemiology of autoimmune diseases. Autoimmun Rev. 2003;2(3):119-125.

Autoimmune Diseases or Flares in Population Vaccinated With COVID-19 Vaccine

According to the MAH, data on the safety of COVID-19 vaccines in patients with autoimmune diseases remain scarce, and studies comparing the consequences of different vaccine types between patients and healthy controls are not available (Boekel 2021).

Class Effect/ other COVID-19 vaccines

The Summary of Product Characteristics [SmPC]) for ChAdOx1-S (recombinant) (Vaxzevria COVID-19 mRNA vaccine (nucleoside modified) (Spikevax SmPC) and COVID-19 mRNA vaccine (nucleoside modified) (Comirnaty SmPC) do not include flare of autoimmune disorders within the product label.

The reference information/labels for all COVID-19 vaccine products mention that there are limited data on immunocompromised people (people with weakened immune systems).

Assessor's comment:

As the MAH points out, data on safety of all the available COVID-19 vaccines in patients with autoimmune diseases are scarce. At present flare of autoimmune disorders is not included in the SmPC for other COVID-19 vaccines at the market.

For Ad26.COV2.S, a safety concern of use in patients with autoimmune or inflammatory disorders is included as missing information in the RMP. The current MAH's core RMP (version 3.0, dated 11 August 2021) also include GBS as an important identified risk and immune thrombocytopenia as important potential risk. Thrombocytopenia (including ITP)have thereafter been concluded to be an important identified risk in the EU-RMP (variation II/18).

Biological Plausibility

Patients of autoimmune conditions are usually under treatment with immunosuppressants. Most of these therapeutics try to control an already hyperactive immune system to lessen the symptoms and relevant organ damage related to autoimmune phenomena. Subsequently, lower immunogenic response or vaccine effectiveness has been observed in patients using eculizumab (McNamara 2017) or oral corticosteroids (Verstraeten 2003). On the other hand, use of vaccines in patients with autoimmune conditions could cause stimulation of a dysregulated immune system (Davidson 2001).

Experience with other vaccinations in patients with autoimmune conditions can be used to gain an insight into the possible relationship between COVID19 vaccination and flares of autoimmune conditions. For example, the annual influenza vaccination could in theory lead to possible stimulation of a dysregulated immune system. However, the MAH states that studies on the effect of influenza vaccination in patients with SLE have shown that vaccination is safe, does not increase the risk of flares and may actually be associated with lower immunogenicity (Herron 1979, Louie 1978, Williams 1978, Brodman 1978, Ristow 1978, Hess 1978, Battafarano 1998, Abu-Shakra 2000, Abu-Shakra 2002). Studies on influenza vaccination in patients with RA have shown similar results (Herron 1979, Chalmers 1994, Mallerson 1993, Caporali 2000, Cimmino 1995). Similarly, exacerbation of MS has not been found for hepatitis B vaccine, tetanus vaccine, and influenza vaccines. (DeStefano 2003, Confavreux 2001).

As stated by the MAH, influenza vaccines are mainly inactivated vaccines and similar deeper body of evidence is not available for viral vector vaccines or live attenuated vaccines. According to the MAH the non-replicating nature of viral vector vaccines may not support a mechanism to cause an added risk of a flare up other than that associated with common infections. However, non-specific inflammatory cutaneous reactions are an expected finding following vaccinations as a broad cytokine release orchestrates the activation of both cellular and humoral components of the immune system (Niebel 2021).

A recent review of possibility of a relationship between both live, inactivated and bacterial vaccination and autoimmune disease concluded that currently there is no evidence of a causal association or biological mechanism between the two. (Olivieri 2021).

Nevertheless, as stated by the MAH, there are proposed pathogenic mechanisms of autoimmune disease following vaccination in the literature described below. These include *molecular mimicry* i.e., the infectious agents (or other exogenous substances) may trigger an immune response against autoantigens and *Bystander activation* by which microbial agents release sequestered self-antigens from host tissue that in turn activate antigen-presenting cells and dormant autoreactive T-helper cells. Autoimmune disorders that have been reported following vaccination are presented in the table below.

Table 2: Autoimmune Disorders Reported Following Vaccination

Autoimmune Disease	Type of Vaccine
Systemic lupus erythromatosus	HBV, Tetanus, Anthrax
Rheumatoid arthritis	HBV, MMR, Tetanus, Typhoid/paratyphoid
Multiple sclerosis	HBV
Reactive arthritis	HBV, BCG, DPT, MMR, Influenza, Typhoid
Polymyositis/Dermatomyositis	BCG, DPT, Smallpox, Diphtheria
Polyarteritis nodosa	HBV, Influenza, Pertussis
Guillain-Barre syndrome	Influenza, Polio, Tetanus
Diabetes mellitus Type 1	HIB
Idiopathic thrombocytopenia	HBV, MMR
Hashimoto thyroiditis	HBV

Key: BCG=Bacillus Calmette–Guerin; DPT=Diphtheria, Pertussis, and Tetanus; HBV=Hepatitis B Vaccine; HIB=Haemophilus Influenzae type B; MMR=Measles, Mumps, and Rubella.
Adapted from Vadalà M, Poddighe D, Laurino C, Palmieri B. Vaccination and autoimmune diseases: is prevention of adverse health effects on the horizon? *EPMA J.* 2017;8(3):295-311.

Assessor's comment:

As stated by the MAH, available data on the effect of inactivated vaccination (such as annual influenza vaccine) in patients with autoimmune diseases indicate that it is safe, does not increase the risk of flares, but may be associated with lower immunogenicity. However, data is scarce for viral vector vaccines and for live attenuated vaccines.

There are also potential pathogenic mechanisms behind flare up and onset of autoimmune disease following vaccination. In the submitted report MAH describes *molecular mimicry* and as *bystander activation*. There are further data indicating non-specific inflammatory cutaneous reactions following vaccinations because of a broad cytokine release which orchestrates the activation of both cellular and humoral components of the immune system.

In an additional literature search by the rapporteur a recent publication including about 6000 patients was found in which the authors observed that infliximab and other immunomodulators, as compared to vedolizumab, was associated with an attenuated serological response to SARS-CoV-2 (Kennedy et al. Gut 2021, not presented by the MAH) indirectly suggesting a suboptimal response to COVID19 vaccine in patients treated with some types of immunosuppressive drugs including anti-TNF products.

To conclude, a biological plausibility behind new onset or/and flares of autoimmune diseases following vaccination against COVID-19 may be considered. By contrast clinical experience and literature do not support that an inactivated vaccine is associated with flare of autoimmune diseases. Corresponding data for viral vector vaccines are scarce.

Product Exposure

In total, an estimated 33,584,049 patients were administered the Ad26.COV2.S vaccine worldwide from to 31 August 2021.

Methods

Non-clinical Data

Results of in-silico sequence homology assessment and the results of non-clinical toxicology study were reviewed to confirm lack of any evidence of flares of immune disorders in preclinical development (appreciating that risk of autoimmune disease in humans is generally difficult to predict from non-clinical data).

Clinical Trial Data

Serious cases reported from the COVID-19 vaccine clinical trials for the Medical Dictionary for Regulatory Activities (MedDRA) Standardised MedDRA Query (SMQ) narrow Autoimmune disorders were reviewed in detail. Cases of encephalitis, acute disseminated encephalomyelitis, transverse myelitis and vasculitis were excluded from the review because they are independently reviewed in the context of a separate evaluation of topics related to these conditions. In addition, it was checked if there was any imbalance for all adverse events included in MedDRA SMQ Autoimmune disorders (narrow) in the pivotal Phase 3 Study, VAC31518COV3001 (data cut-off: 24 August 2021).

GMS Global Safety Database

A cumulative search of the GMS Global Safety database was performed through 31 August 2021 for for the adverse events coded to Standardised MedDRA Query (SMQ) Immune-mediated/autoimmune disorders (narrow).

Literature

An integrated cumulative search of the major biomedical literature databases was performed on 01 September 2021 for all reports/articles relating to the use of COVID-19 vaccines (including Company and non-company COVID-19 vaccines) and autoimmune diseases. The biomedical databases searched included BIOSIS Previews, MEDLINE, Derwent Drug File, and Embase.

Results

Review of Preclinical Data

The MAH stresses that in general, it is noted that autoimmune disease is difficult to predict from non-clinical data as the underlying mechanisms are highly complex.

In-silico sequence homology assessment: A homology assessment was conducted to identify potential sequence homologies of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Spike antigens wtLS-nCoV-dFurin-PP (COR200007) and WHCoV. S.dTM.dFurin.PP.foldon with human protein sequences. According to the MAH, no linear amino acid sequence similarities between Ad26NCOV028 and Ad26NCOV030 transgene inserts and human protein sequences with an E-value of < 10 was observed. Potential causes of autoimmune disease like conformational epitope homologies were not assessed in this analysis.

Non-clinical toxicology: The MAH states that available data from the pivotal GLP toxicology study with did not indicate any signal suggestive of autoimmune conditions, based on the clinical pathology and histopathology evaluation of the major organs and organ systems, that includes, the kidneys, gastrointestinal tract, haematopoietic system (spleen, bone marrow and haematology), skin, endocrine system, musculoskeletal system, nervous system, and vascular system.

Review of Clinical Data

Study VAC31518COV3001 was a randomized, double-blind, placebo-controlled Phase 3 study to assess the efficacy and safety of Ad26.COV2.S for the prevention of SARS-CoV-2-mediated COVID-19 in Adults Aged 18 Years and Older. As of data lock point of 24Aug2021, in the full analysis set (Ad26.COV2.S n= 21898 and placebo n=21890), there were 18 subjects (<0.1%) during the entire double-blind phase, who had at least one event of immune-mediated or autoimmune disorders in the Ad26.COV2.S group as compared to 16 subjects in the placebo group (<0.1%) showing no significant imbalance.

Study VAC31518COV3009 was a randomized, double-blind, placebo-controlled Phase 3 study to assess the efficacy and safety of Ad26.COV2.S for the prevention of SARS-CoV-2-mediated COVID-19 in adults aged 18 years and older. In the full analysis set (Ad26.COV2.S n=15708 and placebo n=15592) during

the entire double-blind phase, there were 9 subjects (<0.1%) who had at least one event of immune-mediated or autoimmune disorders in the Ad26.COV2.S group as compared to 9 subjects in the placebo group (<0.1%) showing no significant imbalance.

In Study VAC31518COV3001, one SAE of GBS and in the study VAC31518COV3009 one SAE of ITP were considered related to the Ad26.COV2.S group. GBS and ITP are both confirmed as ADRs and are not part of this AdHoc (excluded preferred terms from analysis of flare of autoimmune conditions).

Assessor's comment:

According to the MAH there were no signals suggestive of an association with autoimmune conditions in the pre-clinical data. However, as pointed out, autoimmune diseases are difficult to predict from non-clinical data as the underlying mechanisms are highly complex. This is acknowledged.

There was no significant imbalance with respect to immune-mediated or autoimmune disorders in the Ad26.COV2.S group as compared to the placebo groups in the clinical trials. Throughout, the proportions of immune-mediated or autoimmune disorders in the interventional clinical trials was low: <0.1% irrespective of treatment arm. It is noted that in these two clinical trials discussed by the MAH above, the following is an exclusion criterion: "*Participant received an investigational drug within 30 days (including investigational drugs for prophylaxis of COVID-19) or used an invasive investigational medical device within 30 days or received investigational immunoglobulin (Ig) or investigational monoclonal antibodies within 3 months,"*

In addition, according to the EPAR, the following was an exclusion criterion in the pivotal VAC31518COV3001 study *"Clinical conditions (e.g., autoimmune disease or potential immune mediated disease or known or suspected immunodeficiency, or participant on hemodialysis) expected to have an impact on the immune response of the study vaccine. Participants with clinical conditions stable under non-immunomodulator treatment (e.g., autoimmune thyroiditis, autoimmune inflammatory rheumatic disease such as rheumatoid arthritis) may be enrolled at the discretion of the investigator. Non-immunomodulator treatment is allowed as well as steroids at a non-immunosuppressive dose or route of administration".*

Thus, subjects with a more severe autoimmune disease were excluded.

GMS Global Safety Database Review

The search of the GMS global safety database retrieved 746 cases (13 cases from clinical trials[11 were from interventional clinical trials, 2 were from non-interventional] and 733 spontaneous cases) reporting autoimmune disorders in patients who received Ad26.COV2.S through 31 August 2021. Of these, 258 cases reported GBS, and 159 cases reported immune thrombocytopenia. The cases of GBS and immune thrombocytopenia are not further discussed. Of the remaining 329 cases, 67 cases reporting vasculitis, 28 cases reporting transverse myelitis and 10 cases reporting encephalitis are discussed as a separate signal evaluation.

The remaining 224 cases were included for a case level review and the demographics and case characteristics for these 224 cases are presented in the tables below.

Table 5: Distribution of the MedDRA Preferred Terms of Interest for Cases Reporting Autoimmune Disorders With the Use of Ad26.COV2.S Cumulative Through 31 August 2021 (n=224)

Category Adverse Events of Interest	Number of Autoimmune Events[a]
Psoriasis	28
Rheumatoid arthritis	27
Autoimmune disorder	24
Multiple sclerosis	15
Raynaud's phenomenon	14
Systemic lupus erythematosus	12
Psoriatic arthropathy	9
Basedow's disease	9
Colitis ulcerative	9
Neuralgic amyotrophy	6
Crohn's disease	6
Autoimmune hepatitis	6
Sjogren's syndrome	5
Autoimmune thyroiditis	5
Myasthenia gravis	5
Rheumatic disorder	4
Type 1 diabetes mellitus	4
Sarcoidosis	3
Myelitis transverse	3
Still's disease	3
Guillain-Barre syndrome	3
Antiphospholipid syndrome	3
Alopecia areata	2
Autoimmune dermatitis	2
Butterfly rash	2
Coeliac disease	2
Haemophagocytic lymphohistiocytosis	2
Henoch-Schonlein purpura	2
Multifocal motor neuropathy	2
Multiple sclerosis relapse	2
Neuromyelitis optica spectrum disorder	2
Neurosarcoidosis	2
Stiff leg syndrome	2
Vitiligo	2
Total Events	**251 (224 cases)**

Key: MedDRA=Medical Dictionary for Regulatory Activities; n=Number; PT=Preferred Term.

a: A single may report more than 1 autoimmune disorder. Events with Frequency≥2 are captured.

Table 6: Characteristics and Demographics of Cases Reporting Autoimmune Disorders With the Use of Ad26.COV2.S Cumulative Through 31 August 2021 (n=224)

Characteristic		Number of Cases
Source	Spontaneous	221
	Clinical[a]	3
Patient Sex	Male	46
	Female	170
	NR	8
Patient Age (Years)[b] **Mean: 49.8** **Median: 52** **Range: 18 to 79**	18 to 29	20
	30 to 39	27
	40 to 49	43
	50 to 59	62
	60 to 64	24
	65 to 75	21
	>75	4
	Adult	5
	NR	18
Country of Origin	United States of America	190
	Netherlands	10
	Germany	6
	Belgium	5
	France	3
	Italy	3
	Ireland	2
	Spain	2
	Panama	1
	Poland	1
	South Africa	1

Key: n=Number; NR=Not Reported.

a: One case is identified from each study: PPSIMM001960, VAC31518COV3012, COVID-19 LIM.

b: For cases where age was not reported, reported age category has been presented.

Case Review Results

Of the 224 cases, 93 cases (=103 events) reported flare up of autoimmune disorders including flare-up of: psoriasis or psoriatic arthritis (PsA: 21), arthritis (15), autoimmune conditions (12), systemic lupus erythematosus (SLE; 10), ulcerative colitis/Crohn's disease (9), multiple sclerosis (MS; 8), autoimmune thyroiditis (5), skin autoimmune disorders (4), muscular autoimmune disorders (3), Raynaud's phenomenon (3), Type 1 diabetes mellitus (2) and sarcoidosis (1). Of the 93 cases 41 were medically confirmed and 52 medically unconfirmed. The majority of these cases reported serious episodes of flare (79.5%; 74/93). Of the cases reporting sex (79), the majority were reported in females (80.4%; 74/92) which is consistent with the disease profile of autoimmune disorders (Cooper 2003). Of cases reporting patients age (85), a significant proportion occurred in the age group of 50 to 59 years (42.5%; 31/73). One of these 93 cases reported history of COVID-19 infection while remaining 92 cases did not report history or concurrent condition of COVID-19 infections. More than half (51.6%; 48/93) reported a history of multiple allergies, infections, or other autoimmune conditions.

Assessor's comment:

Based on an estimated 33,584,049 individuals who have reviewed the Ad26.COV2.S vaccine worldwide from launch to 31 August 2021, there are in total 224 cases of reported flares and/ or new onset of autoimmune disorders. Of the 224 cases, 93 cases (=103 events) reported flare up of autoimmune disorders: psoriasis or psoriatic arthritis (PSO/PSA: 21), arthritis (15), autoimmune conditions (12), systemic lupus erythematosus (SLE; 10), ulcerative colitis/Crohn's disease (9), multiple sclerosis (MS; 8), autoimmune thyroiditis (5), skin autoimmune disorders (4), muscular autoimmune disorders (3), Raynaud's phenomenon (3), Type 1 diabetes mellitus (2) and sarcoidosis (1).

The review of the cases is made using the reasoning in the WHO-UMC Causality Assessment scale. Since the Ad26.COV2.S. is given as a single dose only, dechallenge/rechallenge is not a factor to consider. Further the time to consider between exposure and an event is uncertain. The most commonly reported drug-induced rheumatic condition i.e., lupus-like syndromes onset is described to develop after weeks to months after start of an inciting medication. By contrast, for idiopathic thrombocytopenic purpura (ITP) following measles, mumps and rubella vaccination, the reported median time to onset is 12–25 days after immunization. The most plausible hypothetical time between Ad26.COV2.S vaccination and the flaring of an autoimmune disorders is unknown (Olivieri et al. Vaccines 2021).

Thus, for this review all events clinically suggesting an autoimmune disease flare occurring the same day as Ad26.COV2.S vaccination or thereafter, are considered to fulfil a temporality criterion. The above discussed uncertainties regarding plausible time relationship and the limited follow-up time for the data presented, are acknowledged limitations.

For reports of new onset of autoimmune diseases in general, no case reviews were provided, making assessments of a causal association impossible. Thus, no assessments of these cases are made and focus throughout the report will be on reported flares.

Arthritis (n=35)

Of the 35 cases reporting arthritis after receiving Ad26.COV2.S, 15 cases reported flare of arthritis and 20 cases reported new onset of arthritis.

Flares (n=15)

Of the 35 cases reporting arthritis after receiving Ad26.COV2.S, 20 cases reported new onset of arthritis and 15 cases (8 medically confirmed, 7 medically unconfirmed) reporting flare of arthritis.

According to the MAH, due to limited information, the causal association between vaccination and rheumatoid arthritis (RA) flare could not be assessed in majority of the cases (66.7%; 10/15), while 1 case reported flares prior to the vaccination making role of Ad26.COV2.S unlikely and in 4 cases the role of the Ad26.COV2.S vaccine in RA flare could not be excluded.

The majority of cases were reported in females (86.7%; 13/15) and of the cases reporting age (14), the majority were reported in the age group of >50 years (78.6; 11/14). This is in line with a prevalence of RA 2 to 3 times higher in women. All 15 cases reported the event of RA and of the 12 cases reporting time to relapse, most of the cases reported the onset of an RA flare within a week after receiving Ad26.COV2.S (75%; 9/12). The outcome for these events was reported as not resolved (8), resolved (4), unspecified (2) and recovering/resolving (1). No pattern of duration of arthritis were, according to the MAH, noted. Of the cases reporting medical history, 50% (7/12) reported a history of multiple allergies and other autoimmune conditions.

Assessor's comment:

Arthritis

Rapporteur's assessment of the 4 cases where a causal association cannot be excluded according to the MAH:

4.1(b) 56-year-old female under treatment with infliximab that experienced RA aggravated *7 days* after the vaccination which took her completely out of remission. Thus, it was reported that at the time the patient was in a complete remission. The patient had the flare for 2 months. She visited the physician's office, but no laboratory tests were performed. The patient had not recovered. Assessed as a **possible association** due to a compatible temporal relationship and the fact that the patient was in complete remission at the time of the vaccination. Limitations include that there was no information/work-up to ascertain other potential aetiology.

4.1(b) 52 -year-old female under treatment with naproxen that experienced a fever of4.1((unit not reported), fatigue, chills, nausea, headache, and debilitating flare of RA on *the same day* as receiving the vaccination. Her fever and chills lasted for 24 hours, and events fatigue, nausea, headache, and debilitating flare of RA lasted for 48 hours. The patient had recovered from the event of interest. Not reported if the patient was in remission prior to the vaccination. Although this case has a reasonable temporality, the combination of described symptoms and the rather prompt recovery makes it more likely that event was caused by more common vaccine reactogenicity. Thus, this case is assessed as **unlikely.**

4.1(b) 46-old-female. Experienced moderate RA pain flared in multiple joints approximately *6 to 7 hours* following the vaccination. The patient experienced arthralgia involving individual knuckles on fingers, wrists, hip, neck, shoulder, knees, and ankles. This was reported as unusual because she typically did not experience pain in a lot of joints at one time. She experienced myalgia, low grade fever (4) (no unit provided), moderate malaise, fatigue, headache, eye pain, mild nausea, abdominal discomfort, and diarrhoea approximately 16 hours post vaccination. The patient could not stay awake. Symptoms were reported as subsided approximately 30 to 32 hours after vaccination and the patient had recovered from the event of interest. Although this case has a reasonable temporality, the combination of described symptoms and the rather prompt recovery makes it more likely that event was caused by more common vaccine reactogenicity. Thus, this case is assessed as **unlikely**.

[redacted]56-year-old-female who experienced RA flare on *Day 1* post vaccination. The patient experienced pain involving knees, ankles, hands, wrists, and feet and fever of 100 degree for 24 hours. Her joint
pain had persisted after 2.5 weeks, and the patient had not recovered from the event of interest. She was reported in
RA remission for 1 year prior to the vaccination. No ongoing RA-treatment. She had a medical history of allergy include mite and food. Assessed as at least a **possible association** based on the clinical picture- The fact that there is no description of verified arthritis is a limitation.

Rapporteur's assessment of the 10 cases not possible to assess due to limited information according to MAH:

For 7 cases it is agreed with the MAH that information is too limited. Notable, for 3 of cases the clinical picture is in accordance with a RA flare having occurred according to the following assessment:

4.1(b) 30-year-old male patient who experienced a flare of RA 8 days post vaccination. Patient
stated that physician said that flare of RA was caused by the COVID-19 vaccine. The outcome of flare RA was not
reported. Unspecified if the patient's RA flare was in remission prior to the vaccination. The event has compatible/suggestive temporal relationship. No available information regarding concomitant medications and medical history or serology provided,
Assessed as a **possible association** based on information given.

4.1(b) 60-year-old female who experienced flare of RA on Day 1 post vaccination. It was reported that she was not able to use her body to full potential, and she experienced pain, her right arm was more affected. She visited the physician's office on an unspecified date and blood test was done. The patient had not recovered from pain and RA. Not reported if the patient's RA flare was in remission prior to the vaccination. No information on RA treatment. Given the temporality and the fact that this could concern a RA flare this is assessed as a **possible association** although the limited information is acknowledged.

4.1(b) 69-year-old male treated with tocilizumab who experienced a RA flare 14 days after the vaccination. The patient experienced pain, arthralgia, soreness, musculoskeletal stiffness, and impaired mobility. The physician was notified and prescribed prednisone for 7 days, and he felt good during that time. However, when tapering prednisone, the flare returned. Blood test for inflammation normal. The outcome was reported as recovering. Unspecified whether the patient´s RA was in remission prior to the vaccination. Due to the temporality and the clinical description assessed as a **possible association**.

To conclude, among the 15 cases retrieved reporting an arthritis flare **5 cases** are assessed as **at least possible association**. Overall, and as described above the high proportion of cases for which an association could not be assessed is acknowledged a limitation (these are not presented in detail).

Psoriasis/Psoriatic Arthropathy (n=33)

Of the 33 cases reporting PSO/PSA after receiving Ad26.COV2.S, 21 cases reported flare and 12 cases reported new onset of PSO/PSA.

Flares (n=21)

Among the 21 cases reporting a flare, 10 were medically confirmed and 11 were medically unconfirmed. In the majority of cases (90.4%; 19/21) a causal association with flare following vaccination could not be evaluated due to limited information, and in 2 cases the role of Ad26.COV2.S in PSO/PSA flare could not, according to the MAH, be excluded. The majority of cases were reported in females (76.2%; 16/21) vs males (23.8%; 5/21). A significant number of cases reported in the age group of 50 to 59 years (38.9%; 7/18) which is line with the typical gender and age distribution of psoriasis/ psoriasis arthritis.

According to the MAH the 21 cases reported 24 events including PSO (n=15) and PSA (n=9) and of the cases reporting time to onset (n=16), most of the cases reported flare of PSO/PSA within a week after receiving Ad26.COV2.S (62.5%; 10/16). The outcome for these events was according to the MAH reported as not resolved (16), resolved (4) and unspecified (4). No pattern of duration of PSO/PSA was noted by the MAH. Of the cases reporting medical history (20), 50% (10/20) reported a history of multiple allergies and other autoimmune conditions. In 15 cases, it was unspecified if the patients had remission PSO/PSA prior to the vaccination, in 5 cases the patients were on immunomodulating medication/antihistamines. However, no remission of PSO/PSA was reported. In 1 case it was reported that the patient's past medical history included psoriasis, and the patient had not taken any medication for many years.

Assessor's comment:

PSO/PSA

Rapporteur's assessment of the 2 cases where a causal association cannot be excluded according to the MAH:

[redacted]A 47-year-old female who experienced worsening of PSA and scalp PSO. Day 1 post vaccination. The patient experienced dizziness about 10 to15 minutes after the vaccine, low full blood count, decreased white blood cell count, and worsening of unspecified condition. Extreme myalgia and arthralgia throughout her body, fever of 102 (no unit provided) for 3 days was also reported as well as several unspecific abdominal and neurological symptoms and **joint flare** (psoriatic arthropathy), scalp PSO. Prednisone and vestibular therapy were prescribed on Day 34 post vaccination with short-term improvement of scalp PSO. Joint pain returned in 3 weeks. The patient still had symptoms including joint flare 8 to 12 weeks post vaccination. The patient had not recovered from the event of interest. In the medical history food drug allergies and other autoimmune conditions (Hashimoto's disease and spondyloarthropathy) were reported and she was on steroids prior to vaccination. Some of the symptoms are more consistent with vaccine reactogenicity. Nevertheless, there is a clinical picture of PSO/PSA flare and a reasonable temporality. This is assessed as a **possible association.**

4.1(b) 56-year old female who experienced PSO flare on Day 17 post vaccination with Ad26.COV2.S. The patient experienced PSO flare including itching all over body, peeling and flaking on scalp, left side and lower back. On an unspecified date, the patient experienced bunch of little spots. Treatment medication included diphenhydramine hydrochloride. The patient had not recovered from PSO flare. Unspecified if the patient's PSO was in remission prior to the vaccination. The event has compatible temporal relationship and a clinical description consistent with a PSO flare. Assessed as **a possible association.**

Rapporteur' assessment of the 19 cases not possible to assess due to limited information according to MAH:

It is agreed with the MAH that for 14 cases information is too limited for any assessment. The remaining 5 cases are assessed as follow:

[redacted]50-year-old female who experienced worsening of PSA on the same day post vaccination. The patient experienced extreme psoriatic arthropathy flare, joint swelling, decreased mobility, and terrible body pain. All symptoms continued for 3 days. The patient also respiratory symptoms that lasted for 6 day. Recovered. Unspecified whether the PSA was in remission prior to the vaccination. Although some of the symptoms coincide with reactogenicity of vaccine there is still a clinical description of joint swelling and temporality. Assessed as a **possible association**.

4.1(b) 60-year-old female who experienced worsening of PSA on the same day as receiving the vaccination. The patient experienced severe PSA flare, erythema, swelling, arthralgia, and pain in extremity (red swollen, painful joints, hands, and feet). The patient visited aphysician; however, no details were provided. Unspecified whether PSA remission prior to the vaccination. Nevertheless, there is a temporality and a clinical description including swollen joints. Assessed as a **possible association**.

4.1(b) Female patient (no age) who experienced worsening of PSO 1 day administration of Ad26.COV2.S. The patient experienced worsening of PSO, skin problem, pain over the entire body, joint pain, cold chills, muscle pain, and fatigue. The outcome was not reported. Unspecified whether PSO was in remission prior to the vaccination. Given the temporality and the clinical description, this is assessed as a **possible association** although the limited information is acknowledged.

4.1(b) 49-year-old female who experienced PSO on Day 1 following vaccination. The patient experienced PSO, chills, and headache and rash. The patient had not recovered from PSO. Whether remission in PSO before vaccination not known. No information on ongoing treatment, medical history or treatment. Limited information is acknowledged but given the temporality and the clinical information this is assessed as a **possible association**.

4.1(b) 58-year-old male who experienced worsening of PSO on 8 days post vaccination with Ad26.COV2.S. The patient experienced pruritus, rash, and urticaria. The patient had recovered. Unspecified whether prior PSO remission. The Although the limited data is acknowledged, there is temporality, and the clinical description of the rash is consistent with PSO event. This is assessed as a **possible association.**

It should also be pointed out that symptoms were in line with a reactogenicity following a vaccination in 7 out of 19 of the cases.

To conclude, among the 21 cases retrieved reporting an PSO/PSA flare following vaccination **7 cases** are assessed as having **a possible association**. For 5 of these cases information on other potential causes to the event or/and treatment/medical history was however limited. For the remaining 14 cases it is agreed with the MAH that data were too limited to assess a causal association (not presented in detail in the report).

Systemic Lupus Erythematosus (n=16)

Of the 16 cases reporting SLE after receiving Ad26.COV2.S, 10 cases reported flare and 6 cases reported new onset of SLE.

Flares (n=10)

Of the 10 cases reporting flare of SLE (6 medically confirmed and 4 medically unconfirmed; 9 serious and 1 nonserious). The MAH states that majority of the cases reported limited information for adequate medical assessment (90%; 9/10) while in 1 case the role of Ad26.COV2.S in SLE flare could not be excluded. Nine of the 9 cases reporting sex were females.

According to the MAH, the 10 cases reported events including flare of SLE (n=8) which occurred within a week after receiving Ad26.COV2.S and butterfly rash (n=2) which occurred in 13 days after receiving Ad26.COV2.S. The outcome for these events was reported as not resolved (n=6), resolved (n=3) and unspecified (n=1). The MAH states that no pattern of duration of SLE were noted.

The majority of the cases (90%, 9/10) reported a history of multiple allergies and other autoimmune conditions. None of the cases reported if the patients had remission SLE prior to the vaccination.

Assessor's comment:

SLE

Rapporteur's assessment of the 1 case where a causal association cannot be excluded according to the MAH:

4.1(b) 50-year-old female who experienced an aggravation of SLE at the same day as the vaccination, with a severe flare of lupus symptoms like joint swelling, pain and swelling. Twenty-three days after vaccination, a lupus anticoagulant test was positive. The patient's symptoms lasted 4 weeks until infusion of drugs (unspecified) was administered, and symptoms were relieved within 2 hours of treatment. The patient recovered from joint swelling, pain, and swelling, and the outcome of condition aggravated, and SLE was not reported. Given temporality, the clinical picture including positivity of lupus anticoagulant test this is assessed as a **probable association.**

Rapporteur's assessment of the 9 cases not possible to assess due to limited information according to MAH:

It is agreed with the MAH for 6 cases information is too limited for any assessment. The remaining 3 cases are assessed as follow:

4.1(b) 78-year-old patient (no sex reported) that three days after receiving vaccine, experienced a typical but worsened autoimmune SLE flare which lasted for 1 month, polyarthritis, condition aggravated, eye swelling, decreased haematocrit, joint swelling, decreased mobility, ocular hyperaemia, rash, fatigue and myalgia. The patient visited the physician's office on an unspecified date. Laboratory data included: haematocrit decreased (low), and white blood cell count decreased (low). Given the temporality and the description of a typical but worse autoimmune SLE flare following vaccination. Unclear if the SLE remission prior to the vaccination. No information on medications. The patient concurrently had Varicella zoster virus infection and infections are known trigger for SLE flare. Thus, this infection might also explain the reaction. Nevertheless, this is assessed as a **possible association**.

4.1(b) 62-year-old female that 4 days after receiving the vaccine, experienced bilateral iritis, a lupus flare
and condition aggravated which at the time of reporting had lasted for over 3 weeks. On an unspecified date the patient visited the physician's office, and an eye exam was performed (results not reported). The patient had not recovered at the time of reporting. No other information was provided. Given the temporality and the event indication autoimmune flare this is assessed as a **possible association** even though the limited information is acknowledged**.**

4.1(b) 20-year-old female that 2 weeks after vaccination experienced a butterfly rash, paraesthesia, pruritus, skin burning sensation, and headache. The patient had not recovered from the events at the time of reporting. No further information was provided. Although the limited and insufficient information is acknowledged it there is a reasonable temporality and the butterfly rash is a typical sign of SLE. This is assessed as **a possible association.**

To conclude, among the 10 cases reporting an SLE flare following vaccination **1 case** is assessed as having a **probable association** and **3 cases** were assessed as a **possible association** although information on other potential causes was to a large extent lacking/limited. For the remaining 6 cases data are too limited to assess a causal association (not presented in detail in the report.)

Multiple Sclerosis (n=16)

Sixteen cases reported events of MS of which, 8 reported flare of MS and 8 reported new onset of MS**.**

Flares (n=8)

Among totally 8 reported flare of MS, 3 were medically confirmed and 5 were medically unconfirmed. According to the MAH 6 cases were assessed to have an indeterminate relationship with vaccination and in 2 cases the causality of the vaccine could not be excluded because of temporal relationship and absence of risk factors.

There were no significant differences by sex of the patients (5 females, 3 males), and the age range was reported as 36 to 71 years (based on 7 cases) with no consistent patterns reported between age groups. These 8 cases reported 8 PTs of interest including MS (7) and MS relapse (2). The time to onset of flare in these cases was reported as ⩽1 week (5), 1 to 2 weeks (2) and >4 weeks (1). The outcome for these events was reported as not resolved (7) and resolving (1) and unspecified (1). None of these 8 cases reported positive COVID-19 test in past or after receiving Ad26.COV2.S.

Assessor's comment:

MS

Rapporteur's assessment of the 2 cases where a causal association cannot be excluded according to the MAH:

4.1(b) 46-year-old female patient who experienced multiple sclerosis, multiple sclerosis relapse, back pain, axillary pain, neuralgia, paraesthesia, hypoesthesia, sensory loss, arthralgia, muscular weakness, pain in extremity 2 days after receiving Ad26.COV2.S. Magnetic resonance imaging and ultrasound of joint was reported as negative (no details provided). The patient had not recovered from the events. It is agreed with the MAH that given temporality and clinical picture causality cannot be excluded. However, since information on patient's medical history is lacking other causes cannot be excluded. This is assessed as a **possible association.**

4.1(b) Male patient (age not reported) who experienced chills few hours after receiving vaccine. The patient was unable to sleep and drank "tons of water". The patient also experienced MS and nausea. The patient had weakness when trying to get around which was accompanied with more nausea. The patient recovered from chills and was recovering from MS and nausea. No further details were reported. The MAH states that in the absence of other risk factors, the causality of the vaccine cannot be excluded. However, the clinical description includes various symptoms not typically for MS flare. If any this might concern a pseudo-relapse. This is **assessed as unlikely.**

Rapporteur's assessment of the 6 cases that had an indeterminate relationship with vaccination according to the MAH:

It is agreed with the MAH for 3 cases information is too limited for any assessment. The remaining 3 cases are assessed as follow:

4.1(b) 46-year-old female who experienced multiple sclerosis, multiple sclerosis relapse, back pain, axillary pain, neuralgia, paraesthesia, hypoesthesia, sensory loss, arthralgia, muscular weakness, pain in extremity 2 days after receiving Ad26.COV2.S. Magnetic resonance imaging and ultrasound of joint was reported as negative (no details provided). The had not recovered from the events. Information on medical history is lacking. Although the limited information is acknowledged this is assesses as a **possible association.**

4.1(b) 49-year-old male who developed bilateral upper and lower extremity weakness and urinary retention 2 days after receiving Ad26.COV2.S. He came into ER and had foley and was subsequently admitted.

He was seen by neurology and started on high-dose steroid x5d for multiple sclerosis exacerbation. Initial MRI showed signs of neuro-inflammation. No new lesions were suggestive of active demyelination. Nine days later, he developed severe bilateral facial weakness and an episode of aspiration. Repeat MRI brain showed new bilateral facial nerve enhancement. Meningitis/encephalitis panel and Lyme CSF were negative. Lyme antibody panel was positive. He was being treated for Lyme disease. Further CSF protein increase, WBC count increase and lumbar puncture abnormal were reported. Treatment medications included: ceftriaxone. The events were unresolved at the time of report. Although it is agreed with the conclusion from MAH that the fact that patients also was diagnosed with Lyme makes a causal association with the vaccine difficult. Nevertheless, the clinical description as well as X-ray and laboratory data is consistent with a flare in MS. This is assessed as **a possible association.**

4.1(b) [redacted] 55-year-old male who experienced MS flare symptoms including difficulty walking and moving the right leg specifically, numbness (about 50% numbness in both legs) 2 months after receiving Ad26.COV2.S. His symptoms of MS had stopped 4 years back and returned at the speed of light after receiving the vaccine. Not recovered. Given temporality and the symptomless MS disease for 4 years prior vaccination as well as a clinical picture consistent with a flare this is assessed as a **possible association.**

To conclude, among the 8 cases reporting an MS flare following vaccination **4 cases** are assessed as having a **possible association**. For 3 of these cases information on other potential causes to the event or/and treatment/medical history was to a large extent lacking. One case is assessed as unlikely. For the remaining 3 cases data are too limited to assess a causal association (details on these not presented in the report).

Raynaud's Phenomenon (n=14)

Fourteen cases reported events of Raynaud's phenomenon of which, 3 reported flare and 11 reported new onset of Raynaud's phenomenon.

Flares (n=3)

According to the MAH, all 3 cases discussed reporting a flare of Raynaud's phenomenon had insufficient information to provide a meaningful medical assessment regarding any potential role of Ad26.COV2.S in the flare of Raynaud's phenomenon. The cases are described below.

Assessor's comment:

Raynaud's phenomenon

Rapporteur's assessment of the 3 cases of reported a flare of Raynaud's phenomenon

4.1(b) Spontaneous case received from a patient via a Regulatory Authority (4.1(b)) concerned a 61-year-old female with a medical history of Raynaud's phenomenon, high cholesterol and arthritis experienced a flare up of Raynaud's phenomenon 14 days after having received Ad26.COV2.S. No concomitant medications were reported. The patient was treated with acetylsalicylic acid. No event outcome was reported. **MAH comment:** In the absence of other risk factors, the causality of the vaccine cannot be excluded regarding the compatible temporal association.

4.1(b) Spontaneous report received from a consumer via a Regulatory Authority [EMEA EVHUMAN NLP,4.1(b)] concerned a 53-year-old female with underlying Raynaud's disease experienced obstinate behaviour, anger, feeling unwell, nausea, fatigue, headache, muscle pain (all nonserious) 1 day after receiving Ad26.COV2.S. Concomitant medications included amlodipine, spironolactone, and hydrochlorothiazide/telmisartan. Two days post-vaccination symptoms of Raynaud's phenomenon were reportedly increasing. At the time of reporting, the patient had not yet recovered from all the symptoms phenomenon and was recovering from headache; the other symptoms had resolved within 1 or 2 days. **MAH comment:** In the absence of other risk factors, the causality of the vaccine cannot be excluded regarding the compatible time to onset. However, further information on patient's medical history needed to exclude other causes.

4.1(b) A spontaneous report received from a patient via a Regulatory Authority [4.1(b)] concerned a 57-year-old female with a medical history of Raynaud's syndrome and drug allergy to sulfacetamide/sulfadiazine/sulfadimidine/sulfamerazine experienced an aggravation of her condition, Raynaud's phenomenon, paraesthesia and cyanosis (all nonserious) 3 months after vaccination Ad26.COV2.S. Concomitant medications included ascorbic acid, ergocalciferol, estradiol, fish oil, levothyroxine, lifitegrast, liothyronine, progesterone, testosterone, triticum aestivum germ oil, and ubidecarenone. The patient had not recovered from the events at the time of reporting. **MAH comment**: In the absence of other risk factors, the causality of the vaccine cannot be excluded regarding the compatible time to onset. However, further information on patient's medical history is needed to exclude other causes.

To conclude, it is overall agreed with the MAH that for the 3 cases reporting a flare of Raynaud's phenomenon following vaccination, information is too limited to make a meaningful assessment of a causal association. However, the cases are few and the clinical picture for all 3 reported cases do not strongly indicate an association.

Colitis Ulcerative, UC /Crohns Disease, CD (n=13)

Thirteen cases reported events of UC/CD of which, 9 reported flare and 5 reported new onset of UC/CD.

Flares (n=9)

Nine (all serious) cases reporting flare UC/CD (3 medically confirmed and 6 medically unconfirmed), 6 concerned females and 3 concerned male patients. According to the MAH 6 of these 9 cases reported limited information for adequate medical assessment (67%; 6/9) while in 3 cases the role of Ad26.COV2.S in UC/CD flare could not be excluded.

Of the cases reporting age (n=8), the age range was 38 to 59 years with most of the cases reported between 50 to 59 year-of age (62.5%; 5/8). Of cases reporting time to onset (6), 4 cases reported a flare within 1 week after receiving Ad26.COV2.S and 2 cases reported a flare 16 days (1) and 17 days (1) days after receiving Ad26.COV2.S. Of the 9 cases, the outcome for events was reported as not resolved (4), resolved (1), resolving (1) and unspecified (3). The majority of these case 82% (5/9) reported a history of multiple allergies while 1 case reported that patient was under stress which has been found to contribute to the progression of IBS (Sun 2019). In 6 cases it was unspecified if the patients had remission of UC/CD prior to the vaccination.

Assessor's comment:

UC/CD

Rapporteur's assessment of the 3 cases where a causal association cannot be excluded according to the MAH:

4.1(b) 59-year-old female that on an unspecified date in the same month as vaccination with developed a fever between 4.1(to 4.1(b On Day 3 post vaccination, the patient started feeling sick and could not move. She developed a rash that started on the same arm where she received the vaccine (left arm), then spreading under her arm to the other arm, neck and shoulder with a burning sensation. On an unspecified date, the patient experienced chest palpitations, chest pain that came and went. Additionally, the patient experienced a consistent headache (her migraines usually went away), sleeping disorder, exhaustion and arthralgia in knee. The patient´s CD had not flared for 15 years. In addition, shortness of breath, a very stressful private situation and a swollen arm at the site of injection are described. It is agreed with the MAH that it is a noteworthy observation that the patient's CD had not flared for 15 years and that a rash within 3 days of vaccination suggests close temporal association. However, the clinical picture describes a wide range of symptoms not typical for CD. So despite temporality this case is **assessed as unlikely.**

4.1(b) 37-year-old male that on an unspecified date, in the same month as receiving Ad26.COV2. experienced fever, aches, and chills, that lasted for 2 nights. During this time the patient took NSAID. However, on Day 17 post vaccination, sharp abdominal pains developed, and an abdominal CT scan showed a UC flare. A colonoscopy confirmed colitis (reported as not severe). The patient's UC that had not flared for 21 years. The patient has recovered. Given temporality and a very clear clinical picture with examinations confirming colitis in a patient with previous UC remission a causal association is reasonable. However, the flare could also be caused by NSAID. To conclude, this is assessed as a **possible association.**

4.1(b) 49-year-old female that within 3 days of vaccination experienced flare of UC and visited the hospital on Day 29 post vaccination. The patient had been in remission for nearly 2 years for UC. Results on laboratory and x-ray data was not reported. The patient had not recovered from the events. Given 2 years of remission and temporality, causality is possible although information is limited" although information is limited. Assessed as a **possible association.**

Rapporteur's assessment of the 6 cases that had an indeterminate relationship with vaccination according to the MAH:

It is agreed with the MAH that for 4 cases information is too limited for any assessment. The remaining 2 cases are assessed as follow:

4.1(b) 52-year-old female that 6 days post vaccination with Ad26.COV2.S, experienced an aggravation of CD. An abdominal CT was done (result not reported). The patient visited the ER and physician office. No further details reported. Although no information on medical history and medications is available the temporality and clinical picture could be consistent with an association. Assessed as a **possible association.**

4.1(b) 49-year-old female that 16 days post vaccination with Ad26.COV2.S, experienced a flare of CD and symptoms of hidradenitis suppurativa worsened. She experienced 2 CD flares in a 1-month span following vaccination. The patient
had not recovered from CD, condition aggravated, and hidradenitis. Given the temporal association and a clinical picture consistent with a CD flare this is assessed as a **possible association** although lack of information on clinical course and diagnostic examinations is acknowledged.

To conclude, among the 9 cases reporting an UC/CD flare following vaccination **4 cases** are assessed as having a **possible association**. For 2 of these cases information on other potential

causes was however to a large extent lacking. For 4 cases data are too limited to assess a causal association. In one case an association is assessed unlikely (4.1(b) [redacted]

Autoimmune Thyroiditis (n=13)

Thirteen cases reported events of autoimmune thyroiditis of which, 5 reported flare and 8 reported new onset of autoimmune thyroiditis.

Flare (n=5)

Of 5 serious cases reporting flare autoimmune thyroiditis (1 medically confirmed and 5 medically unconfirmed), all concerned females. Of the cases reporting age (4), most of the cases reported between 40 to 49 years of age (75%; 3/4). The outcome for these events was reported as not resolved (4) and resolving (1). According to the MAH, four of these 5 cases reported limited information for adequate medical assessment (80%; 4/5) while in 1 case the role of Ad26.COV2.S in autoimmune thyroiditis flare could not be excluded.

Assessor's comment:

Autoimmune Thyroiditis (n=5)

Rapporteur's assessment of the one case where a causal association cannot be excluded according to the MAH:

[redacted]42-year-old female. The narrative starts "Around a month later, her condition aggravated". It is assumed that it should say a month after vaccination. The patient went to the ER with pelvic pressure, exhaustion, swelling, nausea, vomiting, vaginal dryness, depression and her period came a week early. Nine days later, laboratory data included: Anti- thyroid antibodies test, which showed that her thyroid antibodies had gone from 195 to 1,434 (units unspecified). No further details were reported. The patient had not recovered. Given temporality and that the diagnosis is confirmed by laboratory tests this is assessed as a **possible association.**

Rapporteur's assessment of the 4 cases that had an indeterminate relationship with vaccination according to the MAH:

It is agreed with the MAH for 3 cases information is too limited for any assessment. The remaining 1 case are assessed as follow:

4.1(b) [redacted] 42-year-old female who received Ad26.COV2.S vaccine intravenously (incorrect route). On the same day of a relapse of Hashimoto's thyroiditis developed. The symptoms were generalised body aches, extreme fatigue, headache, 7 pounds weight gain, mood swings, bloating, swelling in whole body, vaginal dryness, pelvic pressure and nausea. On Day 44, Anti-thyroid antibody was elevated at 1,434 (unit and normal range not reported) and stool analysis reported as inconclusive. On an unspecified date, anti-thyroid antibody was 195 (unit and normal range not reported). Bacterial and blood test as well as CT and diagnostic ultrasound reported as inconclusive. The patient had not recovered at time of reporting. Given temporality and clinical picture in a patient reported to be in remission since 10 years this is assessed as a **possible association**. The limited information including endocrinologic exam report (baseline and peak TSH, free T4, total T3, thyroid imaging, antithyroid antibodies, viral serology excluding underlying infection etc) is acknowledged. The incorrect route of administration is noted.

To conclude, among the 5 cases reporting a thyroiditis flare following vaccination, **2 cases** are assessed as having a **possible association**. For 1 of these cases information on other potential causes was to a large extent lacking. For the remaining 3 cases data are too limited to assess a causal association (not described in detail in the report).

Muscular Autoimmune Disorders (n=8)

This includes myasthenia gravis (5), stiff leg syndrome (2) and myasthenia gravis crisis (1). Of these 8 cases, 3 reported flare of myasthenia while 5 reported new onset of myasthenia gravis.

Flares (n=3)

The MAH describe that the 3 cases reporting a flare were serious and medically confirmed. All patients were over the age of 70 years. Two were males, one was female. One case reported a history of multiple myasthenia gravis crises prior to vaccination and concomitant use of beta blockers including metoprolol, 1 case reported use of beta blockers including metoprolol. Beta blockers are known to be associated with an aggravation of myasthenia gravis symptoms (UpToDate: Myasthenia Gravis and Drugs that may unmask or worsen myasthenia gravis). Thus, the MAH considers that for these 2 cases an alternative cause to the flare is present. The third case is assessed by the MAH as a possible association. The cases are described below.

Assessor's comment:

Muscular Autoimmune Disorders (n=3)

Rapporteur's assessment of the one case where a causal association cannot be excluded according to the MAH:

4.1(b) A spontaneous case received from a health care professional via 4.1(b) and concerned a 72-year-old male. The patient's past medical history included bladder cancer, bladder stone, benign prostatic hyperplasia, and urinary obstruction. Concurrent conditions included diabetes, hypertension, and myasthenia gravis. No known drug allergies. Concomitant medications included azathioprine, colecalciferol, finasteride, hydrochlorothiazide, lisinopril, pyridostigmine, and tamsulosin. The patient experienced difficulty with chewing, swallowing and speaking 3 days after receiving Ad26.COV2.S. The patient awoke up with paraesthesia/numbness in the face and eating problems. No report of difficulties in breathing or generalised weakness but did experience cough with secretions. The patient was hospitalised for 3 days and underwent intravenous immune globulin treatment for a myasthenia gravis flare. At the time of reporting, the patient's symptoms had been ongoing for 2 weeks with no improvement. Given temporality and clinical picture indicating a myasthenia gravis flare this is assessed as a **possible association.**

Rapporteur's assessment of the 2 cases where an alternative cause was present according MAH:

4.1(b) This spontaneous report was received from a health care professional via 4.1(b) and concerned a 79-year-old male. The patient's past medical history included atrial fibrillation, and concurrent conditions included hypertension, metastatic squamous cell carcinoma in situ, and congenital oculocutaneous albinism. Concomitant medications included acetylsalicylic acid, famotidine, **metoprolol succinate**, paracetamol, prednisone, and white soft paraffin. The patient had a history of myasthenia gravis (MG) with multiple prior myasthenia crises that required intravenous immunoglobulin treatment, with 1 episode requiring intubation. The patient experienced a MG exacerbation with no apparent trigger that began 2 weeks after receiving Ad26.COV2.S. On Day 16, the patient experienced progressive difficulty swallowing, slurred speech, and generalised weakness. The patient's oxygen saturation was lower than normal (92% compared to a baseline of 95%). On an unspecified date, the patient experienced a fall while carrying a tray while using his walking aid. The patient visited the emergency room (ER) and was found to be hypoxic (88%) on arrival. Laboratory results during hospitalisation were leukocytosis (13.68), hyponatraemia to 127 and negative infectious workup (units and normal ranges not provided). A CT of the head was found to be abnormal with chronic microvascular changes and global atrophy, but negative for acute process. The patient was started on a 3-day course of immunoglobulin therapy on Day 35 due to concern for myasthenia gravis exacerbation. The patient also suffered from cerebral small vessel ischaemic disease. **MAH Comment:** The case reported use of beta blockers including

metoprolol which is known to be associated with an aggravation of myasthenia gravis symptoms. (UpToDate: Myasthenia Gravis and Drugs that may unmask or worsen myasthenia gravis).

4.1(b) This spontaneous case concerned a 73-year-old female. The patient's past medical history included hypothyroid, coronary artery disease, gastroesophageal reflux disease, high blood pressure, high cholesterol, and anxiety,
and concurrent conditions included MG, codeine allergy, iodine dye allergy, CT scan dye allergy, myelogram dye allergy and allergy to unknown anaesthesia. Concomitant medications included acetylsalicylic acid, alprazolam, amlodipine, ascorbic acid, biotin, colecalciferol, esomeprazole magnesium, folic acid, hydrochlorothiazide, iron, levothyroxine sodium, **metoprolol,** olmesartan, pravastatin, probiotics, tocopheryl acetate and vitamin B complex. The patient experienced an immediate post-injection reaction and headache after the administration of Ad26.COV2.S. Extreme fatigue began the day after vaccination, which continued until the patient experienced a myasthenic crisis (and was hospitalised 7 days post- vaccination). On admission the patient had dyspnoea and was reportedly close to being intubated. The patient stayed in surgical intensive care for 7 days, followed by 2 days in a regular hospital room. The patient reported the following: negative inspiratory force breathing scores The patient's NIF scores at home ranged from 25 to 30 (no further details reported). **MAH Comment:** The case reported use of beta blockers including metoprolol which is known to be associated with an aggravation of myasthenia gravis symptoms. (UpToDate: Myasthenia Gravis and Drugs that may unmask or worsen myasthenia gravis)

Although agreed with the MAH that betablockers may trigger a flare of MG it is not considered that this can explain the clinical picture in either of the two cases described above. Further, it is not clear whether the patients had been treated with betablockers for a long or short period where a recently started use to a higher extent might have suggested the drug to be a trigger Thus, both cases are considered **a possible association**.

To conclude, number of cases are few although all **3 cases** are assessed as a p**ossible association**. Nevertheless, the signal of an association is weak.

Skin Autoimmune Disorders (n=7)

The 7 cases classified as skin disorders reported MedDRA PTs of interest including Alopecia areata (2), Autoimmune dermatitis (2), Vitiligo (2) and Pyoderma gangrenosum (1). Of these 7 cases, 4 cases were reported flares and 3 cases was reported new onset of skin autoimmune disorders.

Flares (n=4)

According to the MAH, for all the 4 cases reporting flare of skin autoimmune disorder (2 medically confirmed and 2 medically unconfirmed), the causality of the vaccine was not assessable. Causal association is not supported by diagnostic work ups or clinical details except for temporal relationship; most of the cases (3/4) were nonserious and were reported by consumers while the fourth case was serious and reported by physician. However, this case lacked further information regarding symptoms of pyoderma gangrenosum and diagnostic examinations. One of the 4 case reported an off-label IV administration of the Ad26.COV2.S vaccine.

Assessor's comment:

Skin Autoimmune disorders

Rapporteur's assessment of the 4 cases of reported a flare of skin autoimmune disorder

It is agreed with the MAH that for 3 out of 4 of the cases with reported flare, information is too limited to be able to assess a causal association. However, according to the assessor, for one case the clinical picture and the temporality may indicate an association. The narrative of this case is as follows:

4.1(b) This nonserious spontaneous case received from a patient concerned a 28-year-old female with a concurrent condition of vitiligo (and no known allergies or other pre-existing medical conditions) who received vaccine reportedly via intravenous route ("poked needle into left shoulder and took it out, needle did not find the vein, tried another time and injected the COVID vaccine successfully"), representing incorrect route of product administration. On the same day, the patient experienced body pain, injection site and shoulder pain, and fever. The next day, the patient's shoulder turned greenish/red. These symptoms, except injection site discolouration, resolved within 2 weeks. Five weeks post-vaccination, the patient experienced new white small dots on her body turning into patches and already existing patches turning bright white, for which she received treatment with tacrolimus. No concomitant medications were reported. The patient had not recovered from the vitiligo flare at the time of reporting. This is assessed as **a possible association** although limited information on medical history including other potential causes is acknowledged. The incorrect route of administration is noted.

To conclude, one case out of 4 or reported flare of autoimmune skin disorders was assessed as a **possible association.**

Sarcoidosis (n=6)

Six cases reported event of sarcoidosis of which, 1 reported flare and 5 reported new onset of sarcoidosis. Of the new onset cases 3 were medically confirmed and 2 were medically unconfirmed an included neurosarcoidosis (2), sarcoidosis (2) and cutaneous sarcoidosis (1).

Flares (n=1)

One serious case reported flare of Sarcoidosis and is discussed below:

Assessor's comment:

Sarcoidosis

Rapporteur's assessment of the 1 case of reported a flare of sarcoidosis

4.1(b) This case was received from a consumer via 4.1(b) (ID: 4.1(b) and concerned a 75-year-old female with underlying sarcoidosis which was reported to be improving. Eleven days after vaccination, the patient experienced weakness, dyspnoea, and an aggravation of sarcoidosis. The patient was hospitalised for 2 weeks and post discharge, she continued to experience asthenia and weight loss. Approximately 8 weeks postvaccination, the patient died from asthenia, condition aggravated, dyspnoea, sarcoidosis, and weight decreased. It was unknown if an autopsy was performed.
The MAH states that there is no information on any other factors potentially associated with the event.
Causality of the vaccine cannot be established as this case was reported by a consumer and reported missing information regarding event details, diagnostic tests, and autopsy details treatment.

The conclusion of the MAH is acceptable to the Rapporteur.

Sjogren's Syndrome (n=3)

Three serious cases (1 medically confirmed and 2 medically unconfirmed) reported new onset of event Sjogren's syndrome after receiving Ad26.COV2.S

Flares (n=0)

Autoimmune Hepatitis (n=6)

Six cases reported event of autoimmune hepatitis of which all 6 reported new onsets of event. These 6 cases reported events of autoimmune hepatitis in 5 cases and 1 case
reported autoimmune hepatitis with cholangitis sclerosing, and UC.

Flares (n=0)

Peripheral Neuropathies (n=8)

Seven cases (4 serious, 3 nonserious) reported new onset of peripheral neuropathies after receiving Ad26.COV2.S while 1 serious case reported limited information to confirm new onset or relapse of neuralgic amyotrophy. The MAH states that for the purposes of this review, cases with limited information were assessed as new onset.

Flares (n=0)

Assessor's comment:

No flares regarding Sjogren's syndrome, autoimmune hepatitis or peripheral neuropathies were reported, however it should be noted that 4 patients with suspected Sjogren syndrome flare are assessed in the section *Flare of Autoimmune Disorders (Not Elsewhere Classifiable)*

Type 1 Diabetes Mellitus (n=4)

Four cases reported event of type 1 diabetes mellitus of which, 2 reported relapse and 2 cases reported new onset of type 1 diabetes mellitus.

Flare (n=2)

For the two cases of flare reported the MAH believes that one case is not sufficiently documented to allow causality assessment and for the other case an association is unlikely given that symptoms were present already before vaccination.

Assessor's comment:

Type 1 Diabetes Mellitus

It is agreed with the MAH that for the 2 cases reporting flare of diabetes mellitus type 1, one case lacked enough information and for the other case an association is unlikely given reverse temporality. Further the reported cases in relation to the high number of exposed are few. Overall, there are no signals of an association.

Autoimmune Disorders (Not Elsewhere Classifiable) (n=42)

Of these 42 cases, 12 reported relapses and 30 serious cases reported new onset of autoimmune disorders. Five serious cases reported limited information to confirm whether a new onset or relapse of the autoimmune disorder was reported. For the purposes of this review, cases with limited information were assessed as new onset. These 30 cases reported events of autoimmune disorder (16), hemophagocytic lymphohistiocytosis (2), antiphospholipid syndrome (2) and amyloidosis, autoimmune haemolytic anaemia, clinically isolated syndrome, coeliac disease, dermatomyositis, Evans syndrome, glomerulonephritis, immune-mediated adverse reaction, morphoea, multisystem inflammatory syndrome in children (each reported once).

Flares (n=12)

Of the 12 cases reporting flare of autoimmune disorders 3 were medically confirmed and 9 medically unconfirmed: 11 serious and 1 nonserious. According to the MAH, eight of these 12 cases reported limited information for adequate medical assessment (66.7%; 8/12) while in 4 cases the role of Ad26.COV2.S in flare could not be excluded. AEs reported in these cases included flares of autoimmune disorder (8) and Addison’s disease, antiphospholipid syndrome, coeliac disease, eosinophilic oesophagitis, and Sjögrens syndrome. The outcome for these events was reported as not resolved (3), resolved (7) and unspecified (2). According to the MAH, no pattern of duration of autoimmune disorders was noted. The majority of cases 75% (9/12) reported a history of multiple allergies and other autoimmune conditions. The MAH states that eight of these 12 cases reported limited information for adequate medical assessment (66.7%; 8/12) while in 4 cases the role of Ad26.COV2.S in UC/CD flare could not be excluded. However, it is noted that this section is not concerning UC/CD flare, an according to the case table provided by the MAH, only in one case causality could not be ruled out by the MAH.

Assessor's comment:

Autoimmune Disorders (n=12)

Of the 12 patients reporting flares of autoimmune disorders not Elsewhere Classifiable, 4 patients also reported Sjogren's syndrome, and three patients reported autoimmune thyroiditis.

These cases are assessed as followed by the Rapporteur:

4.1(b) /4.1(b) patient reported. A female of unspecified age who experienced a flare of an underlying, not further specified autoimmune disease at an unspecified duration after receiving Ad26.COV2.S vaccine. Symptoms included chills, fever, muscle and joint pain, swelling of hand and face, pain in her wrists, knees, elbows, hands, neck, and shoulders, severe nausea, vomiting, and fatigue, as well as swollen and painful lymph nodes in her armpits and groin area. The patient also reported that she was diagnosed with Sjogren's syndrome by an ophthalmologist. No event outcome was reported. The lack of information regarding temporality and duration and no medical verification of the symptoms and autoimmune disease before the vaccination makes this case **unassessable**, although some of the symptoms (joint pain, swelling of hands, swollen lymph nodes) could be suggestive of a flare of Sjogren's syndrome.

4.1(b) /4.1(b) Patient reported. A female, 39 years old, with a history of Sjogren's syndrome and an unspecified autoimmune disease experienced pain in the right arm and "spinal cord nerves" at the time of vaccination, followed by injection site discomfort, nausea, heat, chills, dizziness, pain in both arms and flush while in the waiting room. The patient also experienced flu-like symptoms for the next 5 days, which included extreme fatigue, overall myalgia, coldness in her extremities, hip pain, decreased appetite, arthralgia, dry eyes, dry mouth, and peripheral neuropathy. The patient also experienced an autoimmune disease flare approximately 2 weeks post vaccination (weight loss, radiating joint pain, severe stomach pain, asthenia, extreme coldness especially her fingers and toes, hip pain, numbness in her fingers, lower back pain, difficulty waking up, inability to do daily tasks, lethargy, and soreness in the morning. alopecia, "pruney" fingers with extreme pain, fatigue). The patient's rheumatologist advised her to take ibuprofen. Approximately 3 months post vaccination, the patient's symptoms noted above remained plus CD4 and CD8 lymphocytes were abnormal, skin was dried, hypovitaminosis, neuralgia, skin wrinkling, stomatitis and white blood cell count increased. No other details were provided. The temporality (2 weeks post vaccination, lasted at least 3 months) and description of the symptoms may be associated with a flare of Sjogrens syndrome (alopecia, dry mouth and eyes, pruney fingers, abnormal lymphocytes, peripheral neurophaty) and thus a **possible association** to the vaccination is reasonable. However, hypovitaminosis is a confounder.

4.1(b) /4.1(b) Spontaneous HCP reported. A female, 55 years old with Sjogren's syndrome who experienced induction of underlying autoimmune disease the day after vaccination which continued for at least 3 weeks. The patient also experienced arthralgia and myalgia which are specific for her Sjogren's flares. The patient had not recovered from arthralgia, autoimmune disorder, myalgia, and pain.
Given temporality (1 day, continued for 3 weeks) and the symptom description regarding arthralgia and myalgia this could indicate a flare from Sjogren's syndrome, however no further information is provided regarding other symptoms, medical examination or diagnostic tests. Both myalgia and arthralgia are also common AEs already described in the SmPC for Ad26.COV2.S vaccine. However, this case has a **possible association.**

4.1(b) /4.1(b) Spontaneous patient reported. A female, 48 years with cerebrovascular disease, Sjogrens syndrome, small fibre neuropathy, Migraine, Muscle disorder, experienced a headache 1 day after receiving Ad26.COV2.S. She was placed on intravenous immunoglobulin treatments and the headaches became uncontrollable. She also developed a rash which she thought was an autoimmune reaction and received shot of ketorolac tromethamine following which rash improved. The patient did not complete any medical tests. The patient recovered from autoimmune disorder, rash and headache and had not recovered from arthralgia and fatigue. Based on the temporality (1 day) and the symptoms (headache and rash, arhralgia and fatigue) and the fact that she was treated with immunoglobulins (although it is not clear for which symptom the treatment was initiated since Immunoglobulin for headache is not an established regimen), a flare of Sjogren syndrome associated with the vaccination is reasonable and thus a **possible association** is considered. However, headache is a common AE already described in the SmPc of Ad26.COV2.S vaccine.

4.1(b) /4.1(b)/Spontaneous patient reported. A female, 46 years with autoimmune thyreoiditis and nervous system disorder had allergy problems the day after receiving Ad26.COV2.S vaccine. The patient had episodes of eczema that were food triggered (condition aggravated), target-shaped rashes and blisters all over her body which was extremely itchy (pruritus). She also complained of arthralgia and paraesthesia. A day later, the patient awoke feeling achy and lethargic. Three days post vaccination, she visited the ER with rash at the injection site and swollen joints. She was given prednisone for 7 days and discharged from the urgent care. "The patient was told that she had an autoimmune response." The patient recovered from autoimmune disorder. It is unclear whether this episode is associated with any flare of autoimmune disease. It is stated that the eczema was food triggered which are a confounder. This case is **unacessable.**

4.1(b) /4.1(b) Spontaneous Patient reported. A female, 60 years old with autoimmune thyroiditis experienced rapid heartbeat (for 24 hours), severe stomach pain, myalgia, arthralgia, "extreme" hypertension and "extreme" fatigue the same day as receiving the Ad26.COV2.S vaccination. CT scan results, and bloodwork were normal except for elevated blood calcium. The patient experienced these symptoms and malaise for several weeks. Three weeks post vaccination, the patient's symptoms were present but lessened in severity and her blood pressure had returned to normal and the stomach pain stopped. The extreme fatigue, muscle pain and joint pain were still present but much better at the time of report. The patient recovered from autoimmune disorder. It is unclear whether this episode is associated with any flare of autoimmune disease. Blood work was normal, it is not stated if thyroid hormone were normal. Due to limited information this case report is considered as **Unassessable.**

4.1(b) /4.1(b) Case concerned a patient with autoimmune thyroiditis who experienced autoimmune flare 1 day after receiving vaccination. The patient also experienced intermittent headaches for a few weeks. The following month, the patient had another autoimmune flare (swollen thyroid and neck). Forty-four days post vaccination, the patient underwent breast biopsy which revealed fibrous mass-benign/a fibroid tissue. The next month, the patient experienced legs hypoaesthesia, increasingly blurred vision, breast tenderness, anxiety and depression, fatigue, and increased weight. The patient's full thyroid panel test revealed increases in values (not specified at the time of the report). No other details were provided. The patient had not recovered from the events. The description of swollen thyroid and neck, elevated thyroid values and the temporality (1 day-several weeks) makes this a **possible association.**

The other 5 cases are assessed by the Rapporteur as follows:

4.1(b) 4.1(b)/Spontaneous/ Case concerned a patient with autoimmune disorder who experienced left-sided severe headache and 3 occasions of left-sided facial numbness approximately 6 days post vaccination. On the same day, the patient's diagnostic results were positive biomarker for autoimmune related disease (normal range not specified), and normal MRI and CT scan. On an unspecified date, the patient's facial numbness resolved, and severity of headache was improved. No other details were provided. The patient recovered from hypoaesthesia, was recovering from headache, and had not recovered from autoimmune disorder. It is unclear which autoimmune disease this patient is suffering from before the vaccination; thus it is not possible to conclude whether this is a flare of autoimmune disease despite the positive temporality. Considered **not assessable**

4.1(b) /4.1(b) Case concerned a patient with a history of lupus and antiphospholipid syndrome who experienced nerve pain throughout her body and headache "right after" vaccination. The patient also reported she experienced sudden "weird stomach pain" on her right side at least 4 to 5 times that day. The next day, the patient awoke with a migraine headache and experienced nausea, vomiting, and sweating. The migraine lasted 3 to 4 days and treatment with sumatriptan was initiated without relief noted. Two days later, the patient consulted with her PCP and rheumatologist, and she underwent a nerve block which helped for approximately 1 month. The patient continued to have migraines and nerve pain. Twenty-eight days later (31 days post vaccination), the patient's doctor told her that she "had greater and lesser nerve block" and "pre-anti-fossid lipid syndrome." Seven days later, results of unspecified blood tests were normal. No other details were provided. Outcome for event of interest was not reported. This case report lacks information regarding diagnostic work up and lacks information regarding outcome. Considered **not assessable.**

4.1(b) 4.1(b) Spontaneous/ 34/male /4.1(b) Case concerned a patient Autoimmune thyroiditis, Addison's disease, Systemic lupus Erythematosus and several allergies who experienced tremors, hyperhidrosis, severe headache photopsia, pain in arm, fatigue, confusion, reduced consciousness, syncope, loss of balance, unable to ambulate or communicate, and adrenal crisis the day after vaccination. The patient was treated at home with oral steroids for Addisons disease at an increased dose ("doubled") for the next few days. The patient's pain and headache lasted longer than other symptoms. Laboratory testing was not performed. No other details were provided. The MAHs conclusion regarding this case is as followed: *Any infection can be a precipitating factor for adrenal crisis. Patients with adrenal insufficiency are considered at increased risk of infections and take longer time to recovery. In literature another adenoviral vaccine ChAdOx-1 has also been reported to have a few cases for adrenal crisis however a clear relationship is not established. Causality of the vaccine cannot be established as this case is missing information regarding clinical course of the events*. *Multiple autoimmune conditions and potential triggers as evident from the concurrent conditions, lack of laboratory data do not provide a clear picture of the event. Considering the temporal association, causality cannot be ruled out.* The patient had several autoimmune diseases. No confirmatory laboratory test was done but the patient was treated with increased corticosteroid dose. The MAHs conclusion that this is a **possible association** is endorsed.

4.1(b) 4.1(b) Spontaneous/ 29/Female/This case is from 4.1(b) (ID not provided) and concerned a patient with a history of eosinophilic oesophagitis who experienced dizziness, bradykinesia, hypoaesthesia, paraesthesia, movement disorder, feeling abnormal, pain, sleep disorder, chills, asthenia, body temperature increased, and myalgia on the same day of vaccination with Ad26.COV2.S. The next day, the patient experienced eye irritation, pain in extremity, fatigue, headache, and mild fever (4.1(b)) and was treated with paracetamol (dose, frequency, duration not specified). Two days later, the patient experienced eosinophilic oesophagitis, dyspnoea, and wheezing. The patient recovered from all the events. No other details were provided. This case is

regarded as **not assessable,** depending on the lack of confirming laboratory tests and no symptom description associated with a flare of eosinophilic oesophagitis

4.1(b) / 4.1(b) Case concerned a patient with a history of **celiac disease** and polymyalgia rheumatica who was undergoing treatment for Hashimoto's disease. The patient experienced coeliac disease and "very little" blister rashes the same day as receiving vaccination. Flu-like symptoms flared up in the afternoon and the rash itched and was painful. The patient applied an unspecified cannabis ointment. The patient still had a few small, dried scabs. Flu-like illness was present for 4 days. The patient recovered from coeliac disease, pain, rash, and rash vesicular, and influenza-like illness and was recovering from scab. Based on insufficient information to assess whether the patient has a flare of celiac disease, PMR or thyroid disease this is considered **not assessable.**

Conclusions: Of the 12 cases reporting flare of autoimmune disorders 3 were medically confirmed and 9 medically unconfirmed. It is noted that although these patients were grouped as autoimmune disorders not elsewhere Classifiable, several patients also had a history of Sjogren's syndrome (4) or autoimmune thyroiditis (3). Overall, 5 of these 12 cases are considered to have a possible association and 3 of these cases were Sjogren patients, however the symptoms described (arthralgia, myalgia and headache) are also common AEs of the vaccine.

Literature review

Overall, the MAH has conducted searches of MEDLINE, Embase, and COVID-19 specific literature aggregator services to identify articles that may inform the benefit-risk profile of the Ad26.COV2.S vaccine. It should be pointed out that the literature includes both flares and new onset of autoimmune diseases included in the report.

Autoimmune Neuromuscular Diseases and COVID-19 Infection

Based on one study (Guidon et al 2020) it is stated by the MAH that data from the current COVID-19 pandemic regarding specific risks and outcomes for patients with neuromuscular disease are unknown and there is a need to be vigilant in assessing neuromuscular patients for potential neuromuscular disease.

Assessor's comment:

It is agreed that based on scarce data no firm conclusions can be drawn.

However, an additional literature search by the rapporteur retrieves 2 case reports of reported flares following COVID19 (not Ad26.COV2.S) vaccination in patients with MG where the author discuss a potential association (Tagliaferri 2021 and Chavez 2021).

By contrast there is also a Chinese publication by Ruan et al. (2021) evaluating MG status after COVID19 vaccination (not specified what type of vaccine) of 22 patients with MG at a single center. In total 20 (90.9%) patients did not present MG worsening within 4 weeks of COVID-19 vaccination whereas two (9.1%) patients reported slight symptom worsening that resolved within a few days. Thus, the study by Ruan et al. does not indicate any strong signal of worsening of MG following COVID19 vaccination.

Multiple Sclerosis

The MAH presents publications on this association that includes 2 case reports, 2 observational studies, and 1 literature review. In an observational study (Achiron 2021) concerning 574 patients with pre-existing MS, the authors conclude that the rate of MS relapse was in alignment with the background incidence of non-vaccinated patients. However, limitations of this study included a short follow-up period. in another prospective observational study (Di Filippo 2021), the authors concluded that the

Pfizer/BioNTech BNT162b2 vaccine did not increase the short-term risk of clinical reactivation of MS. A literature review (Woopen 2021) concluded that MS patients should be vaccinated against SARS-CoV-2, and is expected to be safe in patients with MS. In the paper the authors highlight (as stated by the MAH) that MS patients should be closely surveyed after vaccination, including measuring their humoral and cellular responses to SARS-CoV-2 vaccination.

Assessor's comment:

Overall there are no strong signals of an association between flares of MS following Ad26.COV2.S vaccination from the literature. It should be noted that the studies described to a large part involves also other available COVID-19 vaccines.

It is especially noted that based on 574 patients with pre-existing MS, the Achiron et al concluded the rate of MS relapse was in alignment with the background incidence of non-vaccinated patients.

Psoriasis

Publications involving COVID-19 vaccine administration and new onset/exacerbation of psoriasis include 3 case reports with 2 involving the use of an mRNA vaccine and the other the use of an adenovirus vaccine platform. Nagrani 2021 described 2 patients, 1 experiencing flare and another experiencing new onset after 2 days and 10 days of second dose of COVID-19 vaccine, respectively. Whereas Bostan 2021, described 2 patients who experienced flares after receiving COVID-19 vaccine and concluded that the vaccines against SARS-CoV-2 may exacerbate psoriasis and patients need to be followed up closely. On the contrary, Damiani 2021 described about the 4 cases and concluded that COVID-19 RNA-based vaccine is safe and effective for psoriatic patients undergoing target therapies (immunosuppressants) and does not trigger psoriasis flares. The final publication discussed by the MAH, Sotiriou 2021, described a case series of 14 patients clinically diagnosed as psoriasis symptoms after COVID19 vaccination (50% mRNA technology vaccines and 50% adenovirus vaccine) The authors conveyed that potentially, systemic treatment confers some sort of protection against vaccine-mediated flares of PSO, whereas patients receiving no treatment, or only topical therapy, were more prone to the activation of an inflammatory process leading to new and often extensive PSO lesions. The MAH discuss that a suggested explanation for this is that a Th17-mediated immunologic response underlies the sudden worsening of psoriasis post influenza vaccination and that this is to some extent prevented in treated patients with PSO.

Assessor's comment:

The MAH describes a handful of studies exploring this association with somewhat inconclusive outcome. There are no controlled studies and although the reasoning that ongoing systemic treatment for psoriasis might protect against vaccine-mediated flares of psoriasis (Sotiriou 2021) is an interesting hypothesis, further data e.g. controlled studies based on larger cohorts would be needed to confirm this.

In an additional literature search, by the rapporteur, it is observed that most larger studies concern flares occurring after vaccination for influenza (H1N1) (Gunes-2015), or pneumococcal pneumonia (Kamiya-2019). With respect to studies of COVID19 vaccine an additional recent publication is however found (Musumeci 2021), i.e., not presented by the MAH, that evaluated 50 patients with stable plaque psoriasis and on biological agents that received SARS-CoV-2 vaccine. All patients discontinued their biological agents 10 days before and after each vaccine dose. None of the patients experienced a psoriatic flare.

Cutaneous Lupus Erythematosus (SCLE)

Publications involving COVID-19 vaccine administration and transition of SCLE into SLE (Kreuter 2021) and an exacerbation of SCLE (Niebel 2021) were presented. This includes 2 case reports one involving the use of an mRNA vaccine (Kreuter 2021) and the other, an adenovirus vaccine platform (Niebel 2021). Kreuter et al. concluded that considering the close temporal relationship and absence of other potential trigger factors, it can be speculated that AdV-vaccination with AZD1222 might have caused the shift of SCLE into SLE in the patient. Niebel et al. states that the patient received her second dose as scheduled after 6 weeks and did not experience any adverse reaction.

Assessor's comment:

Overall based on current presented publications there are no strong signals of an association between a flare of SCLE following Ad26.COV2.S vaccination from the literature although the few studies described to a large part involves also other available COVID-19 vaccine. However, data are scarce.

Renal disorders

Publications involving COVID-19 vaccine administration and occurrence of renal disorder include 3 case reports with 2 involving the use of an mRNA vaccine and the other, an adenovirus vaccine platform. Sekar 2021 described the case of ANCA glomerulonephritis followed by second dose of the Moderna vaccine. Perrin 2021 described the case of immunoglobulin A (IgA) nephropathy followed by Moderna vaccine. Aydin 2021 described the relapse of membranous nephropathy 2 weeks after the first dose of Sinovac's COVID-19 vaccine. Finally, 1 literature study, Kronbichler 2021 concluded that the use of COVID-19 vaccines in patients with immune-mediated kidney diseases pose no additional safety issue compared to the use in the general population and that these subjects should be vaccinated.

Assessor's comment:

Data are limited and based on few case reports. The study by Kronbichler 2021 is discussing that the use of COVID-19 vaccines in patients with immune-mediated kidney diseases pose no additional safety issue is based on secondary reference i.e., as reported in one of the recent Phase 3 trials. It should be observed that in the study by Kornbichler et al. members of the Immunonephrology Working Group (IWG) of the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) discuss thirteen frequently asked questions regarding safety and efficacy of the most promising vaccine candidates. Thus, the paper constitutes a literature search and an expert-opinion.

Overall, there are currently no strong signals of an association between renal disorders and vaccination.

Remaining Articles Related to Autoimmune Diseases

The MAH further presents publications involving COVID-19 vaccine administration and occurrence of autoimmune diseases include 7 articles, 4 case reports, and 3 literature studies. Among 4 case reports, 3 were reported due to mRNA vaccine and the other with inactivated SARS-CoV-2 vaccine. In brief these reported flare of RA (1) at the same day as a dose of BNT162b2 vaccine without other obvious cause (Teracina 2021) and Uwaydah 2021 reported a case of multisystem inflammatory syndrome (MIS) the same day after the second dose of an inactivated SARS-CoV-2 vaccine and 6 weeks after COVID-19 infection. The MAH states that this second case likely is related to the COVID infection as most cases of MIS occur several weeks following confirmed or suspected SARS-CoV-2 infection.

Rocco 2021 reported autoimmune hepatitis in a patient with concurrent Hashimoto’s disease 1 week after Pfizer/BioNTech BNT162b2 vaccine with a temporal association and a typical clinical picture and treatment response. Finally, Vera-Lastra 2021 reported 2 cases of Graves' disease 2 days and 3 days after 1st dose of Pfizer-BioNTech BNT162b2 vaccine.

Of the remaining 3 articles, 2 concluded no additional risk and recommended that vaccination should be given in IBD (Kumar 2020), and in SLE and ANCA-associated vasculitis (Sim 2021). The remaining third paper concluded that, currently, no mechanisms have been demonstrated that could explain the correlation between vaccination and the development of autoimmune diseases. Furthermore, epidemiological studies do not support the hypothesis that vaccines cause systemic autoimmune diseases. (Olivieri 2021)

Assessor's comment:

It is acknowledged that literature on the relation between vaccination against COVID 19 and autoimmune disease is limited and mainly based on a handful of case reports. No specific pattern with respect to type of disease has been observed. Regarding the case presented by Uwaydah 2021 it is agreed with the MAH that this case is likely related to the COVID infection rather than to the vaccination.

Overall, no strong signals of an association or any mechanism that could explain a correlation between vaccination and onset and/or flare of autoimmune disease are observed among the publications presented by the MAH.

Post-marketing Reporting Frequency-Observed/Expected cases

As the exact background incidence rates for flare of autoimmune conditions is not well established, as a secondary measure of incidence rate, overall rates of autoimmune conditions were taken into consideration. To support this indirect comparison, the MAH has calculated post-marketing reporting frequency for all autoimmune conditions (not excluding new onset conditions). The frequency for all autoimmune conditions (including new onset conditions and excluding Guillain-Barrés syndrome (GBS), idiopathic thrombocytopenic purpura (ITP), vasculitis, encephalitis and transverse myelitis) is approximately 6.6 cases per million. This is based on 221 spontaneous cases reported for autoimmune disorder and a total exposure of 33,584,049 doses of Ad26.COV2.S vaccine. Thus, the reporting frequency is: 221/33,584,049 cases/unit=6.6x10-6. The background incidence of various autoimmune conditions is spanning from 5 per 100,000 (e.g., chronic active hepatitis, uveitis, Wegener's granulomatosis) to more than 500 per 100,000. The MAH states that there are limitations to this calculation, however, that this calculation is more inclusive and is expected to produce a larger reporting frequency than actual frequency for flare-ups and thus is used for illustrative purposes.

Assessor's comment:

It is noted that the observed/expected (O/E) broad analysis (applying a 100% reporting percentage and point estimate incidence Rate) showed an O/E ratio of <1 across all new onset and/or flares autoimmune disorders. The limitations of the method are acknowledged.

The conclusion made by the MAH

Based on the overall analysis of clinical, literature and post marketing safety data, there is insufficient evidence to conclude that flare of autoimmune disorders is causally associated with Ad26.COV.S. The company will continue to monitor these events through routine pharmacovigilance.

Assessor's overall discussion and conclusion on the relationship between Ad26.COV2.S and autoimmune disorders taking into account data presented within this procedure, cumulative data from clinical trials and post-marketing reporting, literature and mechanistic reasoning

Background

On 16 July 2021 a signal was identified for autoimmune disorders with the use of COVID-19 vaccine AD26.COV2.S based on literature reports of newly diagnosed or flares of autoimmune diseases following vaccination with mRNA vaccines (psoriasis, cutaneous lupus erythematosus, and immunoglobulin 4 (IgG4) related nephritis) and the AstraZeneca vaccine (minimal change disease).

The current product information does not list flare of autoimmune disorders as an adverse reaction for any of the Covid-19 vaccines. For the Janssen Covid-19 vaccine, TTS, GBS, ITP immune thrombocytopenia are included in the PI; and listed among identified risks in the RMP. Additionally, a safety concern of use in patients with autoimmune or inflammatory disorders is included as missing information in the RMP.

Preclinical and clinical data

The MAH presents preclinical data and data from the clinical trials (Phase 3 studies VAC31518COV3001 and VAC31518COV3009) on a potential association. Overall, it is agreed with the MAH that there were no signals suggestive of autoimmune conditions in the pre-clinical data. However, as pointed out, autoimmune diseases are difficult to predict from non-clinical data as the underlying mechanisms are highly complex. This is acknowledged.

Based on the clinical trials there was no significant imbalance with respect to immune-mediated or autoimmune disorders in the Ad26.COV2.S group as compared to the placebo groups. Throughout, the proportions of immune-mediated or autoimmune disorders in the interventional clinical trials was <0.1% irrespective of treatment arm. It is noted that in these two clinical trials discussed by the MAH i.e., *Studies VAC31518COV300* and *VAC31518COV3009,* the following was an exclusion criterion:

"*Participant received an investigational drug within 30 days (including investigational drugs for prophylaxis of COVID-19) or used an invasive investigational medical device within 30 days or received investigational immunoglobulin (Ig) or investigational monoclonal antibodies within 3 months,"*

Thus, subjects with a more severe autoimmune disease were excluded. However, this should not have led to the majority of the population with pre-existing autoimmune diseases having been excluded from the studies.

Biological plausibility for an association

Overall, it is agreed with the MAH that available data on the effect of inactivated vaccination (such as annual influenza vaccine) in patients with autoimmune diseases indicate that it is safe, does not increase the risk of flares, but may be associated with lower immunogenicity. Still, data are scarce for viral vector vaccines or live attenuated vaccines. A recent publication including about 6000 patients however observed that infliximab and other immunomodulators versus vedolizumab was associated with attenuated serological responses to SARS-CoV-2 (Kennedy et al. Gut 2021, not presented by the MAH) indirectly suggesting a suboptimal response to COVID19 vaccine in patients treated with some types of immunosuppressive drugs including anti-TNF agents.

Conversely, vaccine-associated autoimmunity is a well-known phenomenon for a variety of vaccines, possibly attributed to either the cross-reactivity between antigens or the effect of adjuvant. In the submitted report MAH describes *molecular mimicry* and as *bystander activation*. Data further indicate non-specific inflammatory cutaneous reactions following vaccinations. According to the MAH this may be due to a broad cytokine release which orchestrates the activation of both cellular and humoral components of the immune system.

Taken together a biological plausibility behind new onset or/and flares of autoimmune diseases following vaccination against COVID-19 could be possible, but potential mechanisms have not been established, and are so far hypothetical only. By contrast, clinical experience and literature do not support a that inactivated vaccination is associated with flare of autoimmune diseases. Corresponding data for viral vector vaccines are scarce.

Case reviews

Based on an estimated 33,584,049 patients that have reviewed the Ad26.COV2.S vaccine worldwide from launch to 31 August 2021 there were in total 224 cases of reported flares and/or new onset of autoimmune disorders. Of the 224 cases, 93 cases (=103 events) reported flares up of autoimmune disorders including: psoriasis or psoriatic arthritis (PSO/PsA: 21), arthritis (15), autoimmune conditions (12), systemic lupus erythematosus (SLE; 10), ulcerative colitis/Crohn's disease (9), multiple sclerosis (MS; 8), autoimmune thyroiditis (5), skin autoimmune disorders (4), muscular autoimmune disorders (3), Raynaud's phenomenon (3), Type 1 diabetes mellitus (2) and sarcoidosis (1).

The review of all the cases was made using the reasoning in the WHO-UMC Causality Assessment scale. Since the Ad26.COV2.S. is given as a single dose only, dechallenge /rechallenge is not a factor to consider. Additionally, the reasonable time to consider between an exposure and an event is uncertain. The most commonly reported drug-induced rheumatic condition i.e., lupus-like syndromes onset is described to develop weeks to months after start of an inciting medication. By contrast, for idiopathic thrombocytopenic purpura (ITP) following measles, mumps and rubella vaccination, the reported median time to onset is 12–25 days after immunization. The most plausible lag time between Ad26.COV2.S vaccination and a hypothetical flaring of an autoimmune disorders is thus unknown (Olivieri et al. 2021).

For the current review all events clinically imposing an autoimmune flare occurring the same day an Ad26.COV2.S vaccination or thereafter, are considered to fulfil a temporality criterion. The above discussed uncertainties regarding plausible time relationship and the limited follow-up time for the data presented, are acknowledged limitations in the assessment.

Importantly the spectra of autoimmune diseases included in this report are wide, spanning from classic autoimmune rheumatic conditions to neurological disorders, each of which have very different clinical presentations as well as underlying pathological mechanisms. Disorders with ≥ 5 reported cases with flare are therefore presented, and discussed, separately.

Arthritis

There were a total of 15 cases of reported flare of arthritis after receiving Ad26.COV2.S. Overall, the gender or age distribution is observed which is in line with a typical RA distribution. No specific pattern of arthritis was observed. Of note, only for 4 cases the arthritis-diagnosis seemed to be physician confirmed according to the case narratives. Thus, most patients reported arthralgia and more generalized pain, making the assessment of a true RA flare difficult. Overall, it should be pointed out that myalgia, arthralgia and other symptoms associated with natural

reactogenicity associated with any vaccine may make a patient of an autoimmune condition to perceive a flare.

Among the 15 cases, one case reported flares prior to the vaccination making the role of Ad26.COV2.S unlikely whereas in 4 cases, a temporal association was present, and the role of the Ad26.COV2.S vaccination for the RA flare could be possible. However, in the remaining 10 cases where MAH states that assessment is not possible due to limited information this is agreed for 7 of the cases. Notable, for 3 of these cases the clinical picture is in accordance with a RA flare even though information on author causes, medical history etc was limited. Thus, according to the assessor, for 15 cases reporting an arthritis flare **5 cases** are assessed as having at least a **possible association** with the vaccination.

Overall, the high proportion of cases for which an association could not be assessed is acknowledged a limitation. The MAH states that the review of cases with arthritis provide insufficient evidence to provide a causal association of flare of arthritis with Ad26.COV2.S. Also taking into account the large exposure to the vaccine, this conclusion is agreed.

Psoriasis/Psoriatic Arthropathy (PSO/PSA)

Among the 21 reported flares of PSO/PSA, the MAH considered that a causal association could not be excluded in 2 cases and these cases are assessed by the rapporteur as having a possible association to the Janssen Covid-19 vaccine. For the 19 cases where the MAH states that an assessment was not possible due to limited information, this is agreed for 14 cases. The remaining 5 cases are assessed as still having a possible association due to temporality and clinical picture. Overall, no specific pattern of disease flare was observed, and the age and gender distribution were as expected in a PSO/PSA population.

Thus, among 21 cases reporting an PSO/PSA flare, in total **7 cases** are assessed as having a **possible association**. For 5 of these cases information on other potential causes to the event or/and treatment/medical history was however limited. It is also noticed that 7 out the 19 cases with limited information on details presented symptoms also consistent with a more general reactogenicity following vaccination. Something that complicates the assessment.

Previous data have indicated that vaccination in general might be linked to develop of psoriasis, although most reports concerns flare occurring after vaccination for influenza (H1N1) or pneumococcal pneumonia (Gunes-2015, Kamiya-2019). With respect to PSO flares following COVID19 vaccines the MAH presents case reports supporting a possible association (Nagrani and Bostan both 2021) whereas other show no signals of association (Damiani 2021). It could further be hypothesized that a vaccination may ameliorate psoriasis considering that vaccination may induce the T helper 1 stimulation producing high level of TNFα, IFNγ, and IL2 thus leading to inflammation. This is in contrast to the findings of a recent study by Musumeci et al. 2021, not presented by the MAH, that evaluated 50 patients with stable plaque psoriasis and on biological agents that received SARS-CoV-2 vaccine. All patients discontinued their biological agents 10 days before and after each vaccine dose. None of the patients experienced a psoriatic flare

Taken together, the totality of data for PsO/PsA flare including 7 reported cases that are considered to have a possible association with vaccination, also taking into account the large number of subjects exposed, is not considered. sufficient to support a causal association between this type of event and the vaccine.

Systemic Lupus Erythematosus

Among the 10 cases reporting flare of SLE the role of Ad26.COV2.S an association could, according to the MAH, not be excluded in **one case** and this was assessed as a **probable**

association. It is agreed with the MAH that for 6 cases out of the remaining 9 information is too limited for any assessment. However, **3** of these **cases** are assessed as a **possible associated** based on the clinical picture and temporality. In the remaining 6 cases data are too limited to assess a causal association.

In their discussion section the MAH further describes the VACOLUP, a cross-sectional study of tolerance of COVID-19 vaccines in patients with SLE. The authors observed that side-effects after COVID-19 vaccination in patients with SLE are common (around 50%) but do not impair daily functioning in most cases. No difference was noted in the occurrence of side-effects after receipt of mRNA vaccines compared with vaccines with other modes of action. This study analysed a 43-question survey of 696 participants with a self-reported, medically confirmed diagnosis of SLE from 30 countries between 22 March 2021 and 17 May 2021 and found that COVID-19 vaccination appears well tolerated in patients with SLE, with only a minimal risk of flare, if any, including after the mRNA vaccines (Felten 2021).

Overall, the high proportion of SLE cases for which an association could not be assessed is acknowledged a limitation. However the review of cases with SLE and the underlying literature provide insufficient evidence for a causal association of flare of arthritis with Ad26.COV2.S.

Multiple Sclerosis

Among the 8 cases reporting an MS flare following vaccination **4 cases** are assessed as having a **possible association**. For 3 of these cases information on other potential causes to the event or/and treatment/medical history was to a large extent lacking. One case is assessed as unlikely. For the remaining 3 cases data are too limited to assess a causal association

With respect to the literature search on MS provided by the MAH there were overall no strong signals of an association although the studies described to a large part involves also other available COVID-19 vaccine. Thus, data on Ad26.COV2.S. in this aspect are scarce. Notably the study by Achiron et al. based on 574 patients with pre-existing MS, concluded the rate of MS relapse was in alignment with the background incidence of non-vaccinated patients

Overall, the high proportion of cases for which an association could not be assessed is acknowledged a limitation. The review of the few cases with MS flares do not provide sufficient evidence for causal association with Ad26.COV2.S.

Colitis ulcerative/Crohn's disease (UC/CD)

Among the 9 cases reporting an UC/CD flare following vaccination, 4 cases were assessed as having a possible association. For 2 of these cases information on other potential causes was however to a large extent lacking. For 4 cases data were too limited to assess a causal association. In one case an association is assessed unlikely (4.1(b)

Overall, due to a small number of cases reporting flares of UC/CD and the limited information reported in these cases, it is difficult to adequately assess a causal association. Overall, there are no signals of association.

Autoimmune Disorders (Not Elsewhere Classifiable)

Of the 12 cases reporting flare of autoimmune disorders 3 were medically confirmed and 9 medically unconfirmed. A possible association were seen 5 of the 12 cases. It is noted that although these patients were grouped as autoimmune disorders not elsewhere Classifiable, several patients also had a history of Sjogren's syndrome (4) or autoimmune thyroiditis (3).

Although a possible association were seen in 3 of 4 cases of the Sjogren patients, the symptoms described (arthralgia, myalgia, and headache) are also common AEs of the vaccine.

Autoimmune disease with few numbers of reported flares

Raynaud's Phenomenon (n=3), Autoimmune thyroiditis (n=5), Muscular autoimmune disorders (n=3), Skin autoimmune disorders (n=4), Sarcoidosis (n=1) and Diabetes mellitus type 1 (n=2) all reported 5 or less cases of flare.

Among the 3 cases reporting a flare of Raynaud's phenomenon and for the 4 cases of autoimmune skin disorders all had insufficient information to provide a meaningful medical assessment regarding any potential role of Ad26.COV2.S in the flare.

For Myasthenia gravis (MG) there are, as stated by the MAH, numerous studies observing a relationship between active COVID infection and MG exacerbations, whereas literature on myasthenia gravis exacerbation induced by the COVID-19 vaccine are scarce.

However, an additional literature search by the assessor retrieves 2 case reports of flares following COVID19 (not Ad26.COV2.S) vaccination (Tagliaferri 2021 and Chavez 2021). By contrast there is also a Chinese publication by Ruan et al. (2021) evaluating MG status after COVID19 vaccination (not specified exact vaccine) of 22 patients with MG at a single center. In total 20 (90.9%) patients did not present MG worsening within 4 weeks of COVID-19 vaccination, and two (9.1%) patients reported slight symptom worsening that resolved within a few days.
Finally, of the 2 cases reporting flare of diabetes mellitus type 1 one case reported limited information for adequate assessment while the other reported concurrent COVID-19 infection which could be associated to the event of type 1 diabetes mellitus.

Thus, for the above disorders, it is difficult to adequately assess a causal association with Ad26.COV2.S due small number of cases and limited information.

Autoimmune disorders with no reported flares

There were no reported flares Peripheral Neuropathies/Autoimmune Hepatitis/Sjogren's after receiving Ad26.COV2.S vaccine. Thus, in the now submitted data there were no signals of association.

Comments on safety databases and the methods used

As the MAH states, there are some limitations with the data bases and the methods used that needs to be highlighted. The use of safety databases (Company and regulatory databases) implies general under-reporting of post-marketing events and reporting biases. Additionally, the numerator/ denominator data o in the databases, does not reflect the true number of patients exposed, thus it is not possible to calculate the true incidence of an adverse event. These limitations are acknowledged.

The MAH also presents an observed/ expected (O/E) broad analysis (applying a 100% reporting percentage and point estimate incidence Rate) showed an O/E ratio of <1 across all new onset and/or flares autoimmune disorders. This is acceptable although the limitations of the method are noted.

Literature
It is overall agreed with the MAH that most literature reviewed concerned case reports/case series, of which most of the case series articles concluded that COVID-19 vaccine was safe to use in autoimmune diseases and there was no increased risk of flare. In a few single case

reports, the authors concluded an association which was mainly based on close temporal association and absence of risk factors. However, in most of the cases published (as well as in the submitted case reviews) there was insufficient information regarding clinical details, laboratory investigations and medical history etc.

It should also be pointed out that in addition to the literature review provided by the MAH, there are also some more recent publications (identified by the rapporteur) concerning potential flares following vaccination against COVID19 in patients with autoimmune diseases. To summarize, the findings do not indicate more reported adverse effects in patients with autoimmune rheumatic diseases as compared to non-autoimmune rheumatic conditions (Cherian et al., Sattui et al. and Rotando et al. all 2021). Sattui et al. presents results from the COVID-19 Global Rheumatology Alliance Vaccine Survey, including 2,860 adults with systemic rheumatic diseases who received various COVID-19 vaccination (Ad26.COV2.S 1.7%). The most common systemic rheumatic disease was rheumatoid arthritis (42.3%), and 81.2% of respondents were on a disease-modifying anti-rheumatic drugs (DMARD). Rheumatic disease flares that required medication changes occurred in 4.6% and these were similar across type of vaccine. Overall, the results did not signal increased risk of flares after COVID-19 vaccination requiring change in medication. Of note, the study had several limitations including a significant proportion of patients deciding to change their medication use (28.9%) to increase vaccine efficacy, as well as a potential selection bias since individuals with adverse events might be more likely to fill out the survey.

Conclusion

On 16 July 2021 a signal was identified for based on literature reports. A cumulative review of flare of autoimmune disorders has now been presented by the MAH and based on that, the MAH concludes that there is insufficient evidence to conclude that flare of autoimmune disorders is causally associated with their vaccine. The current SmPC does not include any information with regard to this issue and the MAH proposes no such SmPC updates within the current procedure.

It should be acknowledged that the MAH's review includes a number of cases describing flares of different autoimmune diagnosis that are assessed as having at least a possible association with the vaccine, in total 35 cases (e.g., 5 arthritis cases, 7 PSO/PSA cases and 4 SLE cases). The limited information in many of the cases *not* assessed as having a possible association should also be noted. Further, it was overall observed that in many of the cases presented, the symptoms included arthralgia, myalgia and fever, i.e., common general vaccination reactions rather than a verified true flare in an arthritis. This is an important aspect for the overall assessment.

Although a biological plausibility behind new onset or/and flares of autoimmune diseases following vaccination against COVID-19 could be possible, potential mechanisms have not been established, and there are no non-clinical/literature data to clearly point at a specific mechanism for such an association for Janssen Covid-19 vaccine.

Further, in the clinical trials (VAC31518COV3001, full analysis set: Ad26.COV2.S n= 21898 and placebo n=21890 and VAC31518COV3009, full analysis set: Ad26.COV2.S n=15708 and placebo n=15592) there was no significant imbalance with respect to immune-mediated or autoimmune disorders in the Ad26.COV2.S group as compared to the placebo groups. Throughout, the proportions of immune-mediated or autoimmune disorders in the trials was <0.1% irrespective of treatment arm which is considered a low proportion.

Finally, the number of reported flare cases are considered low in relation to the estimated exposure of the vaccine (approx. 33,584,049 subjects have received the Ad26.COV2.S vaccine worldwide from launch to 31 August 2021). Although it is not possible to estimate how many of

those who could have had an autoimmune disease, it may be assumed that a substantial number of subjects with underlying autoimmune disease can have been exposed to the vaccine since there are no restrictions regarding vaccination in this population.

Based on the above, it is agreed with the MAH that there is at present not sufficient support for a causal association between Ad26.COV2.S and flares of autoimmune disorders.

2.2.1.2. Closed Signals That are Categorized as Important Identified Risks

Thromboembolic Events (TBE) With Thrombocytopenia

Request: On 04 April 2021, a signal was identified for TBE with thrombocytopenia [subsequently referred to as Thrombosis with Thrombocytopenia Syndorme (TTS)], with the use of Ad26.COV2.S based upon EMA's PRAC request.

Rapporteur assessment comment:

TTS has been evaluated in depth within the signal procedure EPITT 19689, and have continuously been followed in the MSSRs.

Guillain-Barré Syndrome

On 05 May 2021, a signal was identified by the MAH based on disproportionate reporting for GBS with the use of Ad26.COV2.S. On 07 July 2021, this signal was re-opened based on a request from the US FDA. On 12 July 2021, the MAH submitted a type II variation (no 12) to update the PI in relation to GBS.

Rapporteur assessment comment: Based on the results obtained in the MAH's signal evaluation, GBS has been included in the SmPC section 4.4 and 4.8 (II/0012). Routine PhV is considered sufficient ahead.

2.2.1.3. Closed Signals That are Categorized as Important Potential Risks

Thrombocytopenia

On 04 April 2021, a signal was identified based on disproportionate reporting for thrombocytopenia events, in particular for MedDRA (version 24) PTs of 'Immune thrombocytopenia' and 'Thrombotic thrombocytopenic purpura' following the use of Ad26.COV2.S in SMART.

Rapporteur assessment comment:

Based on repeated evaluations within MSSRs, and in a Type II variation (II/0020), ITP has been included in the SmPC section 4.4 and 4.8 with the frequency not known. The PRAC has also concluded that thrombocytopenia should be an important identified risk for the Janssen covid-19 vaccine. Updates of the RMP is ongoing within II-18.

Capillary Leak Syndrome

On 15 June 2021, a signal was identified for the event of CLS with the use of COVID-19 Vaccine Ad26.COV2.S, based on the identification of 3 cases from post-marketing experience of CLS following vaccination with Ad26.COV2.S.

Rapporteur assessment comment: On 18 June, the MAH sent an ESI to EMA regarding CLS. It was thereafter assessed within type II variation 0010, which resulted in updates of the product information and also a DHPC.

2.2.1.4. Closed Signals That are Identified Risks not Categorized as Important

During this reporting period, the following signals have been closed and are identified risks not categorized as important. Additional details can be found in Appendix 3.

Hypotension

Hypotension falls within the vaccine-anxiety related reactions. This topic is also discussed also in Section "Vaccination Anxiety-Related Reactions".

Rapporteur assessment comment: A warning regarding the possibility of anxiety related reactions that may comprise vasovagal syncope is included in section 4.4 of the SmPC. No safety concern regarding isolated hypotension has been observed with the vaccine. The closure of the signal is endorsed.

Diarrhoea

On 22 April 2021, a signal was identified based on disproportionate reporting for diarrhoea with the use of Ad26.COV2.S.

Rapporteur assessment comment: Diarrhoea has been included in the SmPC section 4.8 as an adverse event (II/0014). The closure of the signal is supported

Dizziness

Dizziness falls within the vaccine-anxiety related reactions. This topic discussed in Section "Vaccination Anxiety-Related Reactions".

Rapporteur assessment comment: Dizziness has been included in the SmPC section 4.8 (uncommon, II/0020)

Loss of Consciousness

Loss of consciousness falls within the vaccine-anxiety related reactions. This topic is discussed in Section 15.4 "Vaccination Anxiety-Related Reactions".

Rapporteur assessment comment:

No new safety concern is detected with loss of consciousness. The closure of the signal is endorsed.

Lymphadenopathy

On 22 April 2021, a signal was identified based on disproportionate reporting for lymphadenopathy with the use of Ad26.COV2.S. There is a reasonable plausibility of an association between the occurrence of lymphadenopathy and the use Ad26.COV2.S.

Rapporteur assessment comment:

Lymphadenopathy has been included in the SmPC section 4.8. as a rare event in the frame of procedure II/0014. A closure of the signal is endorsed.

Tinnitus

Tinnitus falls within the AESI of sensorineural hearing loss (SNHL). During the evaluation of case data from the MSSR for April 2021, the broad O/E analysis for the AE of SNHL was found to be higher than expected for the 18 to 59 years age group, with the majority of the cases reporting the PT Tinnitus (O/E ratio 1.01 [95% CI: 0.0663-1.486]14). The MAH then considered is sufficient evidence to establish a causal association between Ad26.COV2.S and tinnitus.

Rapporteur assessment comment:

Tinnitus has been concluded as vaccine related in one of the MSSRs and has been included as rare event in section 4.8 of the SmPC (MEA14.2; MEA14.3; II/0014). The closure of the signal is endorsed.

Cutaneous Sensory Changes

On 22 April 2021, a signal of cutaneous sensory changes was identified based on disproportionate reporting for sensitive skin, hypoaesthesia, and paraesthesia with the use of Ad26.COV2.S Based on cumulative reviews through 17 May 2021, paraesthesia and hypoaesthesia are considered associated with the use of Ad26.COV2.S.

Rapporteur assessment comment:

Paraesthesia (uncommon) and hypesthesia (rare) have been added to the SmPC section 4.8 in the frame of procedure II/0014. The closure of the signal is endorsed.

Vomiting

On 22 April 2021, a signal was identified based on disproportionate reporting for vomiting with the use of Ad26.COV2.S. Based on this review of post-marketing data through 24 May 2021, vomiting is considered associated with the use of Ad26.COV2.S.

Rapporteur assessment comment:

Vomiting (rare) has been added to the SmPC section 4.8 in the frame of procedure II/0014. The closure of the signal is endorsed.

Anxiety-Related Reactions

On 22 April 2021, a signal was identified based on disproportionate reporting for anxiety-related reactions

with the use of Ad26.COV2.S. An association between the occurrence of anxiety-related reactions (including dizziness, low blood pressure) as and the vaccination is considered reasonable.

Rapporteur assessment comment:

A warning regarding anxiety related reactions is included in the SmPC of Janssens vaccine. Additionally, anxiety related reactions such as dizziness have been added to the SmPC section 4.8. No new safety concern is detected here, and the closure of the signal is endorsed.

2.2.1.5. Closed Signals That are Potential Risks not Categorized as Important

During this reporting period, the following signals have been closed and are potential risks not categorized as important. Additional details can be found in Appendix 3.

Vasculitis

On 06 August 2021, a signal was identified by the MAH for vasculitis, which was based on receipt and review of an autopsy report for case report 4.1(b) The autopsy report confirmed a latency of 11 days between the receipt of the COVID-19 vaccine and the first diagnosis of vasculitis. Further, it confirmed that vasculitis was among the causes of death for the patient.

MAH Conclusion: A cumulative review was conducted and included in the September MSSR. Based on the post-marketing spontaneous reports, isolated cases of biopsy confirmed vasculitis with close temporal relationship following the vaccination of Ad26.COV2.S (e.g., <2 weeks) have been reported. However, in consideration of the large number of the exposure of Ad26.COV2.S (e.g., 33.5 million doses administered), lack of preclinical MOA, no numerical imbalance from the 2 large phase 3 double-blinded, placebo-controlled clinical trials, as well as the extremely rare post-marketing spontaneous reporting rate compared with the background rates, the MAH considered there is insufficient evidence to conclude a clear causal association between vasculitis and Ad26.COV2.S. The MAH continues to monitor these events and provide updated assessment when additional data become available. Additional information on this evaluation can be found in Appendix 7.15, Vasculitis.

Rapporteur assessment comment:

In the MSSR for September 2021, evaluation of the data submitted for vasculitis raised concerns, and further review was requested for the October MSSR. Following further evaluation (in MEA 14.7) it was concluded to add "small vessel vasculitis" in section 4.8. of the section SmPC. Furthermore, the MAH has been requested to continue to follow up on vasculitis with focus on cases of vasculitis with systemic signs

Transverse Myelitis

Request: In the PRAC AR dated 02 September 2021 regarding the MSSR of Ad26.COV2.S covering the period of 01 July 2021 to 31 July 2021, the EMA made further requests for transverse myelitis. Additional data was assessed in the August 2021 MSSR (AR dated 30 September 2021)

Rapporteur assessment comment:

In the frame of MEA 14.6 (September 2021 MSSR), which was after the cut-off for this PSUR, it was concluded to update the SmPC with transverse myelitis in an upcoming type II variation

(EMEA/H/C/005737/II/0035), based on a review of cumulative and interval data presented by the MAH. The closure of the signal can be endorsed.

Encephalitis

Request: In the July 2021 MSSR AR dated 02 September 2021, the Rapporteur considered that:
"(...) the O/E data above raise further concerns, and it is considered warranted to undertake an in-depth review in the upcoming MSSR. Thus, a cumulative review of encephalitis including ADEM should be provided in the MSSR covering the month of September, which is due on 15th October 2021, also taking available data from literature and clinical studies into account.
This should include an O/E analysis where e.g., photophobia cases only, have been removed (as presented in the MSSR of June 2021). A discussion on the need for a label update should be provided as well."
MAH Conclusion: A cumulative review on encephalitis has been covered together within the analysis performed for transverse myelitis. Additional information on this evaluation can be found in Appendix 7.16, Transverse Myelitis and Encephalitis (Including ADEM).

Rapporteur assessment comment:

Encephalitis including ADEM has been thoroughly investigated based on reviews of cumulative and interval data in MSSRs (MEA 14.6, MEA 14.7), it has been concluded that the available data so far not allow a firm conclusion on causality. Continued monitoring is requested for upcoming SSRs and PSURs

2.2.2. Ongoing Signals and regulatory authority requested topics

2.2.2.1. Ongoing Signals

The evaluation of VTE was concluded during the preparation of this report. Additional details can be found in Section 14, Late-Breaking Information. Evaluations were completed for flare of autoimmune disorders, vasculitis, and transverse myelitis/encephalitis and reports are attached with this PBRER. These reports contain additional details on the evaluation results (see Appendix 7.5, Autoimmune Disorders; Appendix 7.15, Vasculitis; and Appendix 7.16, Transverse Myelitis and Encephalitis including ADEM) respectively. These signals are being closed and at this time, the status of ongoing is only procedural.

Rapporteur assessment comment:

Vasculitis should continuously be followed (see above), as well as encephalitis including ADEM. See further details above.

2.2.2.2. Regulatory Authority Requested Topic (Not Considered a Confirmed Signal)

Olfactory Disorder

As requested in EMEA/H/C/005737/MEA/014.: "It is noted that cases of olfactory disorders are listed in the summary tables. The MAH is requested to present a thorough presentation (including O/E analysis) of

the cases within the next MSSR." Additional information on this evaluation can be found in the MSSR with a reporting period of 01 April 2021 to 30 April 2021.

Rapporteur assessment comment:

In the MSSR covering April 2021 (EMEA/H/C/005737/MEA/014.1) the MAH had executed a search regarding olfactory disorders in their global safety database, which resulted in 38 cases. Based on this review, it was agreed that no clear evidence of safety concern is detected here at this stage.

Acute Generalized Dystonia

On 02 August 2021, during a telephone call with the Moroccan PV centre, Company participants on the call noted the following information: Since the start of vaccination with Ad26.COV2.S in Morocco, in total 7 cases reporting AEs were received (including 1 fatal case). The observations were described by the Moroccan PV Centre participants as follows: i) The events occurred within 15 minutes after vaccination, ii) The reported events were upper chest discomfort, plafonnement du regard' (traduced to fixed upward gaze, extremities stiffness-rigidity which was referred to as similar to post neuroleptic effect; iii) the patient who passed away was transferred to an intensive care unit with cyanosis of the face, followed by 3 episodes of convulsions. The patient did not respond to benzodiazepines and died from heart failure; iv) In the same intensive care unit, another patient was already admitted with chest discomfort and needed oxygen. The latter events were considered an anxiety crisis; v) The same day of first vaccinations, a Health Care Professional (HCP) called the PV centre reporting a person with hypoesthesia of lower body which resolved spontaneously; vi) Information on this evaluation can be found in the MSSR with a reporting period of 01 July 2021 to 31 July 2021, Section 9.2.7., Acute Generalised Dystonia.

Rapporteur assessment comment:

In the MSSR covering July 2021 (EMEA/H/C/005737/MEA/014.4) a review of dystonia was presented. The cumulative review, initially identifying 7 cases, and after further detailing, it appears that two may have been dystonia. It was agreed that based on this information, no further action is justified at present, and routine PhV is sufficient.

Requests for the current PSUR

The following requests were posed in the MSSRs: Even if these requests may not be possible to address in the initial PSUR submission, the MAH should prepare responses to the following points; which will have to be addressed in responses to the preliminary PSUR AR.

1. **Neuralgic amyotrophy:**

In France, 3 medically confirmed case reports (including 3 serious cases) of neuralgic amyotrophy (NA) were identified in the national PV database. The MAH is asked to present a cumulative review of neuralgic amyotrophy cases in the next MSSR, including details of the underlying condition(s), time to onset, duration, outcome and an assessment of the causal relationship with the vaccine. Based on this review, a discussion on the need to update the product information should be provided, if applicable.

A cumulative review covering neuralgic amyotrophy was provided in the MSSR EMEA/H/C/005737/MEA/014.7 (data cut-off 18 October 2021), but is assessed in this PSUR.

Case definition used by MAH

For the purposes of this report, the following four criteria were applied to each of the cases in order to determine whether a case was considered to represent neuralgic amyotrophy, based on the following diagnostic criteria (van Alfen 2015).

- New onset of acute/subacute shoulder pain
- Pain score ≥7 (scale of 0-10)
- Abnormal shoulder movement/winged scapula
- Monophasic course with slow recovery

A case with all 4 criteria is considered a definite case; with 3 criteria is considered a probable case; with 1 or 2 criteria is a possible case. If the patient had preceding trauma, malignancy, diabetes mellitus and radiation, the case is excluded.

Results

Literature
The literature search did not retrieve any reference article for NA following Janssen COVID-19 vaccine use.

Data mining in health authority (VAERS/EudraVigilance) and Company databases
The PT Neuralgic amyotrophy met the threshold for disproportional reporting in 1 of the 2 external databases (EudraVigilance). This PT also met the threshold for disproportionality in the GMS global safety database. The other 4 PTs of interest (brachial plexopathy, brachial plexus injury, radiculitis brachial, and peripheral nerve injury) did not meet the threshold for disproportionality in either of the external databases or in the GMS global safety database.

Clinical trial data
No cases of NA were reported in any of the MAH sponsored clinical trials (DLP 31October 2021).

Review of reported cases in GMS Global Safety Database
The cumulative search of the GMS global safety database as of 18 October 2021 retrieved a total of 14 spontaneous cases of NA following Ad26.COV2.S. Of the 14 reports, 1 serious case (4.1(b) from 4.1(b) contained multiple unidentifiable patients; thus, this case will not be further discussed and has been excluded from the analysis. Of the remaining 13 cases, 69% (9/13) were serious and 77% (10/13) were medically confirmed.

Of the 13 patients, 46% (6/13) were female and 54% (7/13) were male. Ages ranged between 31 and 75 years, who experienced NA with a time to onset of 1 day to 75 days.

The time to onset (TTO) was reported within the 28-day risk window in 61% (8/13) of cases as follows: 1 day (n=2), 5 days (n=1), 8 days (n=1), 11 days (n=1), 13 days (n=1), 17 days (n=1) and 22 days (n=1) following vaccination with Ad26.COV2.S. The remaining 5 cases reported the TTO as 30-, 41-, and 75-days following vaccination; the TTO was unknown in the remaining 2 cases.

No cases with a fatal outcome was reported. Of the 13 cases, 61% (8/13) were not resolved, 8% (1/13) were resolving, 8% (1/13) resolved, and in 23% (3/13) of the cases the outcome was not provided at the time of reporting.

Six of the 13 cases met the case definition of NA. Of the 13 patients, 23% (3/13) reported a relevant and possible confounding medical history which included: trigeminal neuralgia in addition to shoulder tendon tears/bursitis/capsulitis (n=1), neuralgia, polymyalgia rheumatica (n=1), and acromioclavicular (AC) joint arthrosis (n=1).

The majority of the cases contained limited information which excluded relevant clinical data including supportive diagnostic testing, clinical course, concomitant medications/vaccinations, concurrent condition/relevant medical history, duration of the event, outcome, and treatment, precluding a thorough medical assessment.

Details of the 13 cases reporting NA received cumulatively to 18 October 2021 have been summarized in table 6 below:

Table 6: Spontaneous Cases of Neuralgic Amyotrophy Following Vaccination with Ad26.COV2.S Captured in the Global Safety Database Cumulative to 18 October 2021 (n=13)

AER Number Age (Years)/Gender Country Medically Confirmed (Yes/No)	Event PT[a] /Event Seriousness	Latency (in days) / Duration of event	Event outcome[b]	Concomitant Drugs/ Treatment	Relevant Medical History	Brief Description/ MAH Comments
Diagnostic Criteria Met = 4						
4.1(b) 60/F 4.1(b) Yes	1) Bursitis/Serious 2) Tendonitis/Serious 3) Nervous system disorder/Non-serious 4) *Neuralgic amyotrophy/Non-serious* 5) Tendon rupture/*Non-serious* 6) Hypokinesia/*Non-serious* 7) Injection site reaction/*Non-serious* 8) Limb injury/*Non-serious* 9) Post-traumatic pain/*Non-serious*	1 day/NR	NR	NR/ ibuprofen, gabapentin, cortisone injection, lidocaine, and triamcinolone acetonide	Trigeminal autonomic cephalgia (left facial pain syndrome), Myalgia following treatment with atorvastatin calcium.	Approximately 1 day following vaccination with Ad26.COV2.S, the patient experienced headache and local symptoms at the vaccination site (left arm). An unspecified time later she developed: bicep pain which traveled to the trapezius and shoulder, numbness of 4th and 5th finger, pectoral spasm, burning sensation (pain 6-7/10), inability to lift, carry, or make coordinated movements. She then developed a loss of grip; she lost her job after about 7 weeks post-vaccine due to inability to use her hand. She could not lift a glass of water or use a keyboard. She developed profound weakness and severe shoulder pain. All symptoms were on the left side. A transcutaneous electrical nerve stimulator and ice seemed to help initially. Eight weeks after vaccination, x-ray of the left shoulder/humerus revealed mild arthritis in left shoulder and AC joint, and no osteomyelitis. Eleven weeks after vaccination, MRI of left shoulder revealed small partial tears of supraspinatus and subscapularis tendons, mild subacromial and subdeltoid bursitis, labrum tear, synovitis. Adhesive capsulitis was ruled out. Orthopedic surgeon believed the patient had a chemically or immunologically related bursitis of the left shoulder, and 13 weeks after vaccine, she was given a cortisone injection in the bursa, with minimal immediate but temporary relief. Course stabilized at about 16 weeks post-vaccine. The patient reported the diagnosis of PTS 24 weeks after vaccination. Twenty-six weeks after vaccination, the physician stated that the patient could now hold a manilla notepad up in her hand, which was an improvement. The patient was recovering from tendonitis/small partial tears of supraspinatus and subscapularis tendons, bursitis, soft tissue of the left shoulder injury, and pain to scapula. Outcome of PTS was unknown. According to the reporting physician the EOI was considered non-serious. ***MAH Comment**: All 4 diagnostic criteria were met: The patient has shoulder pain, rated 6-7/10, abnormal shoulder movement and weakness, a monophasic course with stabilization and the first signs of recovery. This is considered a definite case per van Alfen 2015 criteria. Based on the temporal relationship a causal relationship is considered possible to vaccine.*
Diagnostic Criteria Met = 3						
4.1(b) 48/Male 4.1(b) Yes	1) Muscular weakness/Serious 2) Paraesthesia/Serious 3) Neuralgia/Serious 4) Dyspnoea at rest/Serious 5) Autoimmune disorder/Serious 6) *Neuralgic amyotrophy/Serious* 7) Neuropathic muscular atrophy/Serious	3 weeks	Not Resolved	NR/ NR	NR	Three weeks following vaccination with Ad26.COV2.S, the patient experienced PTS, further described as "ipsilateral with partial high position of diaphragm." An unspecified time after vaccination, the patient also experienced muscle weakness, short term arm tingling, neuralgia (described as unbearable pain), dyspnoea at rest and on exertion, autoimmune disorder, denervation

	8) Dyspnoea exertional/Serious 9) Decreased activity/Serious 10) Musculoskeletal discomfort/Serious 11) Muscle atrophy/Serious					atrophy, decreased activity, shoulder discomfort, and muscle atrophy of left shoulder girdle. EOIs were ongoing at the time of reporting. No diagnostic data was provided. ***MAH comment**: Three of 4 diagnostic criteria were met: The patient has shoulder pain, described as unbearable, abnormal shoulder movement with muscle atrophy, and diaphragmatic involvement. Details around clinical course/recovery are not provided. Based on the symptoms consistent with NA in this medically confirmed case, this is considered a probable case per van Alfen 2015 criteria. While there is limited information regarding clinical course, concomitant medications, concurrent/relevant past medical history, laboratory/imaging data, and treatment information, based on the temporal relationship of the reported event to vaccine, a causal relationship is considered possible to vaccine.*
Diagnostic Criteria Met = 2						
4.1(b) 53/Female 4.1(b) No	1) *Neuralgic amyotrophy /non-serious*	11 days/Not Applicable	Not Resolved	Cetirizine, omeprazole, and paroxetine/ NR	NR	Approximately 11 days following vaccination with Ad26.COV2.S, the patient experienced severe pain of the right arm/shoulder. Subsequently, she was diagnosed with an acute attack of NA which was considered non-serious by the reporting consumer. ***MAH Comment**: Two of 4 diagnostic criteria are met: The patient describes pain of the arm and shoulder described as severe. Shoulder movement and clinical course are not described. Although the case is not medically confirmed, it appears the diagnosis was given to the patient, presumably from a medical professional. Based on the symptoms consistent with neuralgic amyotrophy, this is considered a possible case per van Alfen 2015 criteria. While there is limited information regarding clinical course, concomitant medications, concurrent/relevant past medical history, laboratory/imaging data, treatment information, and outcome, based on the temporal relationship with vaccination, the causal relationship is considered possible to the vaccine.*
Diagnostic Criteria Met = 1						
4.1(b) 57/Male 4.1(b) Yes	1) *Neuralgic amyotrophy/Serious* 2) Paresis/*Serious*	8 days/Not Applicable	Not Resolved Not Resolved	NR/ NR	NR	Approximately 8 days following Ad26.COV2.S, the patient experienced NA and paresis in arms. The EOIs were ongoing at the time of reporting. No diagnostic data was provided. ***MAH Comment**: One of 4 diagnostic criteria are met: This case noted arm paresis, with the diagnosis of neuralgic amyotrophy. Pain, pain score, and clinical course are not described. While there is limited information regarding clinical course, concomitant medications, concurrent/relevant past medical history, laboratory/imaging data, treatment information, and outcome, based on the temporal relationship with vaccination, this case is assessed as a possible case per van Alfen 2015 criteria and. the causal relationship is assessed as possible to vaccine due to temporal relationship.*

4.1(b) 64/Female 4.1(b) Yes	1) Vaccination site pain/Serious 2) Arthralgia/Serious 3) Paraesthesia/Serious 4) Pain/Serious 5) *Neuralgic amyotrophy/Serious*	1 day/Not Reported	Resolved with Sequelae	Not Reported/ Not Reported	Five months prior to onset of the event, she was vaccinated with Fluarix Tetra.	Approximately 1 day following vaccination with Ad26.COV2.S, the patient experienced acute pain in the left shoulder that radiated laterally up to the middle of the arm and in the axillary area. She was hospitalised and diagnosed with PTS. Diagnostic Data was not provided. It was reported that the patient recovered with sequelae (unspecified). ***MAH Comment**: One of 4 diagnostic criteria are met: This case describes new onset acute shoulder pain, with the diagnosis of NA. Pain score, shoulder movement and clinical course are not described. Based on the symptoms consistent with NA in this medically confirmed case, this is considered a possible case per van Alfen 2015 criteria. While there is limited information regarding clinical course, concomitant medications, concurrent/relevant past medical history, laboratory/imaging data, treatment information, and outcome, based on the temporal relationship with vaccination, the case is considered possibly related.*
4.1(b) 75/Male 4.1(b) Yes	1) *Neuralgic amyotrophy/Serious* 2) Inflammation/Serious 3) Muscular weakness/Serious 4) Pain in extremity/Serious	5 days/Not Applicable	Not Resolved	NR/NR	NR	Approximately 5 days following vaccination with Ad26.COV2.S, the patient was diagnosed with NA in addition to right arm pain and weakness secondary to brachial plexus inflammation. At the time of reporting, the events were ongoing. Information regarding treatment was not provided. ***MAH Comment**: One of 4 diagnostic criteria are met: This case describes new onset arm pain and weakness, with the diagnosis of neuralgic amyotrophy. Pain score, shoulder movement and clinical course are not described. Based on the symptoms consistent with NA in this medically confirmed case, this can be considered a possible case. While there is limited information regarding clinical course, concomitant medications, concurrent/relevant past medical history, laboratory/imaging data, treatment information, and outcome, based on the temporal relationship with vaccination, the case is considered possibly related.*
Diagnostic Criteria Met = None						
4.1(b) 58/Female 4.1(b) Yes	1) *Neuralgic amyotrophy/Serious*	30 days/NA	Not Resolved	NR/ NR	NR	Approximately 30 days following vaccination with Ad26.COV2.S, the patient was hospitalised secondary to PTS. The EOI was ongoing at the time of reporting. No diagnostic data was provided. *MAH Comment: None of the specific diagnostic criteria, shoulder pain, pain score, shoulder movement or weakness, and clinical course, are provided. Although this is a medically confirmed case providing the diagnosis of PTS, it cannot be considered a true case without additional information. This case lacks pertinent details of the clinical course, medical history, laboratory or imaging data, and outcome thus precluding an adequate medical assessment. Company causality is indeterminate.*
4.1(b) 31/Female 4.1(b) No	1) Nervous system disorder/Serious 2) *Peripheral nerve injury/Serious* 3) Dizziness/Non-serious 4) Muscle spasms/non-serious 5) Parosmia/Non-serious 6) Walking aid user/non-serious 7) Vomiting/Non-serious 8) Pain/Non-serious 9) Dyspnoea exertional/non-serious	41 days/Not Applicable	Not Resolved/ Not Resolved	NR/ Prednisone	NR	Approximately 41 days following Ad26.COV2.S, the patient experienced difficulty walking. She was diagnosed with central and peripheral nerve damage associated with extreme pain, burning in feet, hands and fingers, and toes. Treatment with Prednisone was administered. At the time of reporting, the EOIs were ongoing. No diagnostic data was provided. ***MAH Comment**: None of the diagnostic criteria are met: This patient describes pain in hands and*

						fingers, feet, and toes. Shoulder pain, pain score, shoulder movement and clinical course are not noted, and TTO is 41 days. This does not appear to be a case of neuralgic amyotrophy. This case lacks pertinent details of the clinical course, medical history, laboratory or imaging data, and outcome thus precluding an adequate medical assessment. Company causality is indeterminate.
4.1(b) 71/M 4.1(b) Yes	1) Neuralgia/non-serious 2) *Neuralgic amyotrophy/non-serious*	17 days/Not Applicable	Resolving	NR/NR	Neuralgia/ Polymyalgia rheumatica	Approximately 17 days following vaccination with Ad26.COV2.S, the patient experienced Parsonage-Turner syndrome. ***MAH Comment:*** *None of the specific diagnostic criteria, shoulder pain, pain score, shoulder movement or weakness, and clinical course, are provided. This cannot be considered a true case of NA without additional information. This case lacks pertinent details of the clinical course, medical history, laboratory or imaging data, and outcome thus precluding an adequate medical assessment. In addition, the patient's medical history includes neuralgia and polymyalgia rheumatica, which are potentially confounding. Company causality is indeterminate.*
4.1(b) 57/Male 4.1(b) Yes	1) *Neuralgic amyotrophy/Serious*	22 days/Not Applicable	Not Resolved	NR/ NR	NR	Approximately 22 days following vaccination with Ad26.COV2.S, the patient was hospitalised secondary to PTS SARS-CoV-2 test was reported as negative. EOI was ongoing at the time of reporting. No diagnostic data was provided. ***MAH Comment****: None of the specific diagnostic criteria, shoulder pain, pain score, shoulder movement or weakness, and clinical course, are provided. This cannot be considered a true case of NA without additional information. This case lacks pertinent details of the clinical course, medical history, laboratory or imaging data, and outcome thus precluding an adequate medical assessment. Company causality is indeterminate.*
4.1(b) 48/Male 4.1(b) Yes	1) *Neuralgic amyotrophy/Serious* 2) Myofascitis/Serious	NR	Not Resolved	Not Reported/ Not Reported	Concurrent back pain	On an unspecified date following vaccination with Ad26.COV2.S, the patient was hospitalised secondary to Neuralgic amyotrophy and Myofascitis. Electromyogram of the shoulder muscles: no abnormalities. MRI/thoracic spine: no abnormalities. It was reported that "oedema was visible in the rhomboid-region, suggesting surmenage (over exertion), MRI of cervical spine and plexus brachialis: no abnormalities." At the time of reporting, the event was ongoing. Information regarding treatment was not provided.

						MAH Comment: None of the specific diagnostic criteria, shoulder pain, pain score, shoulder movement or weakness, and clinical course are provided. Although this is a medically confirmed case providing the diagnosis of PTS, it cannot be considered a true case without additional information. This case lacks pertinent details of the clinical course, medical history, laboratory or imaging data, and outcome, as well as the TTO, thus precluding an adequate medical assessment. Company causality is indeterminate.
4.1(b) 40/Male 4.1(b) No	1) *Neuralgic amyotrophy* /non-serious	75 days/Not Applicable	Not Reported	Not Reported/Not Reported	Not Reported	Approximately 75 days following vaccination with Ad26.COV2.S, the patient experienced brachial plexitis (right arm). Laboratory/Diagnostic data was not provided. It was reported that Lyme Disease and a cerebrovascular accident was ruled out. Electromyogram confirmed brachial plexitis which was considered related to Ad26.COV2.S per the reporting consumer. ***MAH Comment**: None of the specific diagnostic criteria, shoulder pain, pain score, shoulder movement or weakness, and clinical course, are provided. This is a medically unconfirmed case; although the diagnosis of brachial plexitis is provided, it cannot be considered a true case of NA without additional information. The TTO was greater than the 28-day risk window. This case lacks pertinent details of the clinical course, medical history, laboratory or imaging data, and outcome thus precluding an adequate medical assessment. Company causality is indeterminate.*
4.1(b) 52/F 4.1(b) Yes	1) *Neuralgic amyotrophy/non-serious* 2) Full blood count normal/non-serious 3) Mobility decreased/non-serious 4) X-ray limb abnormal/non-serious 5) Osteoarthritis/non-serious 6) Pain/non-serious 7) Red blood cell sedimentation rate normal/non-serious 8) Vaccination complication/ non-serious 9) Arthralgia/ non-serious 10) Pain in extremity/ non-serious 11) Headache/non-serious 12) Fatigue/non-serious	13 days/Not Applicable	Not Resolved	ergocalciferol prednisone, sertraline, and trazodone/ Not Reported	Depression/ anxiety	Approximately 13 days following vaccination with Ad26.COV2.S, the patient experienced neuralgic amyotrophy, osteoarthritis, pain, red blood cell sedimentation rate normal, vaccination complication, arthralgia, and pain in the extremity. An X-ray of the limb revealed mild degenerative AC joint arthrosis. Treatment was not reported. At the time of reporting, the event was ongoing. ***MAH Comment**: None of the specific diagnostic criteria, shoulder pain, pain score, shoulder movement or weakness, and clinical course are provided. This cannot be considered a true case of NA without additional information. This case lacks pertinent details of the clinical course, medical history, laboratory or imaging data, and outcome thus precluding an adequate medical assessment. In addition, the patient's current x-ray demonstrated mild degenerative AC joint arthrosis, which is potentially confounding. Company causality is indeterminate.*

Abbreviations: AC=Acromioclavicular; AER#=Adverse Event Report Number; EOI=Event of Interest; MRI=Magnetic Resonance Imaging; NA=Neuralgic Amyotrophy; NR=Not Reported; PT=Preferred Term; TTO=Time to Onset; US=United States.
a: The MedDRA PT of interest has been italicised.
b: The outcome has been presented for the event of interest only.

<u>O/E Analysis</u>

A broad O/E analysis with sensitivity analysis was performed for the United States (US) and European Union (EU), stratified by age groups: 18-59 and ≥60 years old. In the broad analysis, the O/E ratio for both age groups in the US and EU was less than 1 for Ad26.COV2.S, indicating that NA does not demonstrate increased reporting when compared to the background rate.

Table 7: Broad O/E and Sensitivity Analysis Results- Neuralgic Amyotrophy

Broad O/E Analysis					Sensitivity Analysis	
Region	Age Range (Years)	Observed Count[a]	O/E Ratio (95% CI)[b,c] (PE, 100% RP)		O/E Ratio (95% CI)[b,c] (LB, 50% RP)	
US	18 to 59	2.65	0.125	(0.022, 0.388)	0.559	(0.100, 1.738)
	≥60	2.34	0.204	(0.031, 0.677)	0.855	(0.130, 2.835)
EU	18 to 59	6.92	0.300	(0.120, 0.621)	1.345	(0.537, 2.782)
	≥60	2.07	0.206	(0.026, 0.730)	0.863	(0.110, 3.059)

Key: CI=Confidence Interval; EU=European Union; LB=Lower Bound; O/E=Observed versus Expected; PE=Point Estimate; RP=Reporting Percentage; US=United States.

a: Counts included cases with events of interest that occurred within the risk window (1-28 days), and cases where time-to-onset was 0 or not reported.

b: Background incident rate generated by Janssen, Internal assessment (27-Oct-2021)

c: Poisson exact confidence interval (95% CI).

Table 8: Restricted O/E and Sensitivity Analysis Results- Neuralgic Amyotrophy

Restricted O/E Analysis					Sensitivity Analysis	
Region	Age Range (Years)	Observed Count[a]	O/E Ratio (95% CI)[b,c] (PE, 100% RP)		O/E Ratio (95% CI)[b,c] (LB, 50% RP)	
EU	18 to 59	4.00	0.174	(0.047, 0.445)	0.777	(0.212, 1.990)

Key: CI=Confidence Interval; EU=European Union; LB=Lower Bound; O/E=Observed versus Expected; PE=Point Estimate; RP=Reporting Percentage; US=United States.

a: Counts included cases with events of interest with known time-to-onset that occurred within the risk window (1-42 days) only.

b: Background incident rate generated by Janssen, Internal assessment (05-Nov-2021)

c: Poisson exact confidence interval (95% CI).

MAH Conclusion:

Based on this cumulative review, there is insufficient evidence to establish a causal relationship between the NA and the administration of Ad26.COV2.S. Key factors to support this conclusion include the low number of cumulative cases in the GMS global safety database, the very low number of well-documented cases assessed as related, lack of consistent evidence of disproportionality across multiple platforms, and no association between the Janssen vaccine and NA identified in the scientific literature. The Company will continue to monitor NA via routine pharmacovigilance.

Rapporteur assessment comment: The cumulative review identified 13 spontaneous cases of NA in the global safety database. Of the 13 cases reported, 3 contained medical history, or risk factors that could have contributed to the occurrence of the event. Of the 13 cases, 1 was classified as definite, 1 probable, 4 possible based on the criteria van Alfen 2015. Due to the temporal relationship (event occurring between 1 to 21 days after vaccination), causality was assessed by the MAH as possible for these 6 cases, which can be agreed. The O/E analyses were <1. Despite some cases with a temporal relationship to vaccination, and thereby assessed as possible, it is at this stage agreed that there is insufficient evidence to allow conclusion on causality. Routine PhV is also agreed.

2. Autoimmune hepatitis

The MAH will be asked to add an in-depth review of autoimmune hepatitis focusing on well-described cases with plausible TTO in the upcoming PSUR.

Autoimmune Hepatitis

Six cases reported autoimmune hepatitis. All 6 reported new onset autoimmune hepatitis, and no case reported flares of autoimmune hepatitis after receiving Ad26.COV2.S.
Of these, 5 cases reported autoimmune hepatitis and 1 case autoimmune hepatitis with cholangitis sclerosing, and UC. Five of these
concerned female patients which is consistent with the fact that autoimmune hepatitis is about
4 times more common in females than males. The age was reported in
5 cases (1 case being 35 years, 4 cases between 50 to 58 years). Four of reported TTO within a week of receiving Ad26.COV2.S, while in the remaining 2 cases, the patient was diagnosed with

autoimmune hepatitis 29 days and 115 days post vaccination, respectively. The outcome was reported as not resolved (4), resolved (1), and unspecified (1). None of the
6 cases reported prior or concurrent COVID-19 infection. One case reported history of allergies including tegaderm allergy, nausea when treated with ampicillin, itching when treated with chlorhexidine, and stomach-ache when treated with acetylsalicylic acid and concurrent conditions of asthma, Hepatitis B and chronic RA.

Rapporteur assessment comment: The MAH has summarized 6 cases of new onset of autoimmune hepatitis without presenting the cases in depth. The MAH is requested to complete the cases with narratives and present a thorough evaluation of these cases (see request for supplementary information).

3. Serious Hypertension

Eighteen serious cases of hypertension (on a total of 30 cases of hypertension) have been reported to date in France. The MAH is requested to present a cumulative review focused on serious hypertension, including details of any underlying condition(s) (including COVID-19), time to onset, duration and outcome, together with an assessment of the causal relationship with the vaccine and a discussion on the need to update the product information, if applicable.

Rapporteur assessment comment: A thorough presentation is missing in the PSUR. The MAH is requested to present and discuss any cases that occurred during the reporting interval in depth with this PSUR (request for supplementary information)

4. Severe Cutaneous Adverse Reactions

Per the final PRAC assessment report for the June MSSR (EMEA/H/C/005737/MEA/014.3), a cumulative review of AGEP and DRESS was requested. Additional information on this evaluation can be found in the MSSR with a reporting period of 01 July 2021 to 31 July 2021, Section 9.2.2, Severe Cutaneous Adverse Reactions.

Rapporteur assessment comment: In MSSR covering July 2021 (EMEA/H/C/005737/MEA/014.4) a cumulative review of AGEP and DRESS was provided by the MAH. It was agreed that there was insufficient support for a causal relationship with SCARs, including SJS or DRESS and the Covid-19 vaccine Janssen. An overview was requested in the upcoming PSUR. In the provided overview one case of DRESS and one case of Stevens-Johnson Syndrome (SJS) and no case of acute generalized exanthematous pustulosis was presented. Even though there was a limited number of cases identified (no new cases compared to the MSSR 014.4), these items should be closely monitored in the future. An updated overview is requested for the next PSUR.

2.3. Evaluation of risks and new information

2.3.1. New Information on Important Identified Risks

Anaphylaxis

During this reporting period, 178 (108 medically confirmed and 70 medically unconfirmed) cases reporting anaphylaxis were identified. All of the 178 cases were serious and reported a total of 180 serious events. Of these 178 cases, 3 were reported from open-label studies and 175 from post-marketing sources (including spontaneous and solicited cases). None of the cases were reported from placebo-controlled studies.

Table 41: Frequency Distribution of MedDRA PTs of Interest Involving the Use of Ad26.COV2.S and Reporting Anaphylaxis (Events=178)

MedDRA PTs	Number of Serious Events
Anaphylactic reaction	102
Anaphylactic shock	29
Shock	19
Anaphylactoid reaction	18
Circulatory collapse	12
Total	**180**

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term.

MAH Conclusion

Based on the review of the literature (i.e., Section 11), ongoing/completed clinical studies (i.e, Sections 7, 8, and 9), and relevant cases retrieved from the Company global safety database for the current reporting period, no new safety information was identified during the reporting period for the important identified risk of anaphylaxis.

Rapporteur assessment comment: During the reporting interval 178 cases of anaphylaxis have been reported, all of them serious and a majority was reported post-marketing. In the SmPC section 4.4 it is stated that events of anaphylaxis have been reported, anaphylaxis is also included in section 4.8 of the SmPC at frequency unknown (included already at the initial authorization). In this PSUR, no new information has been provided regarding anaphylaxis that alters the previous assessments.

Rapporteur assessment comment: During the reporting interval 178 cases of anaphylaxis have been reported, all of them serious and a majority was reported post-marketing. In the SmPC section 4.4 it is stated that events of anaphylaxis have been reported. It is also stated that appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following the administration of the vaccine, and that the subject being vaccinated should be under close observation for at least 15 minutes following vaccination. Furthermore, anaphylaxis is also included in section 4.8 of the SmPC at frequency unknown (included already at the initial authorization).

In this PSUR, no new information has been provided regarding anaphylaxis that alters the previous assessments. This risk is well known in clinical practice and within the vaccination campaigns in the Member States. Based on the current post marketing experience, the conclusion at approval that routine risk minimisation is sufficient to mitigate this risk is maintained. Of these reasons, it is also no longer considered in need of further characterisation within the ongoing PASS programs. Taken together, while anaphylaxis remains an identified risk for the product, as with any other biologicals, it does not have an

impact on the benefit / risk balance of the vaccine. Therefore, anaphylaxis should be reclassified as not "important", and removed from the summary of safety concerns in the RMP at the next regulatory opportunity. This event is expected to be monitored via routine pharmacovigilance.

Thrombosis with Thrombocytopenia Syndrome (TTS)

During this reporting period, 206 (164 medically confirmed and 42 medically unconfirmed) cases reporting TTS were identified. Of these 206 cases, 205 were serious and 1 was nonserious reporting a total of 454events (451 serious, 3 nonserious). Of these 206 cases, 10 were from placebo-controlled studies, 3 were reported from open-label studies, and 193 from post-marketing sources (including spontaneous and solicited cases).

Rapporteur assessment comment: TTS has been evaluated in depth during the reporting interval in signal EPITT 19689; EMEA/H/C/005737/II/0006/G; and in the MSSRs EMEA/H/C/005737/MEA/014.1 - 07 TTS is included in section 4.4 & 4.8 of the SmPC (and the PIL accordingly). In this PSUR, no new substantial information has been provided regarding TTS.

Guillain-Barré Syndrome

During this reporting period, 255 (159 medically confirmed and 96 medically unconfirmed) cases reporting GBS were identified. All of the 255 cases were serious reporting a total of 263 serious events. Of these 255 cases, 2 were from placebo-controlled studies, 1 was reported from an open-label study, and 252 from post-marketing sources (including spontaneous and solicited cases).

Table 46: Frequency Distribution of MedDRA PTs of Interest Involving the Use of Ad26.COV2.S and Reporting Guillain-Barré Syndrome (Events=263)

MedDRA PTs	Number of Serious Events
Guillain-Barre syndrome	239
Chronic inflammatory demyelinating polyradiculoneuropathy	7
Demyelinating polyneuropathy	6
Miller Fisher syndrome	6
Subacute inflammatory demyelinating polyneuropathy	4
Bickerstaff's encephalitis	1
Total	**263**

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term.

Rapporteur assessment comment: In EMEA/H/C/005737/II/0012, the product information was updated (SmPC section 4.4 and 4.8; PIL accordingly) to address GBS. The RMP was to be updated with GBS as an important identified risk In this PSUR, no new information has been provided regarding GBS that alters the previous assessments.

2.3.2. New Information on Important Potential Risks

Vaccine-Associated Enhanced Disease Including Vaccine-Associated Enhanced Respiratory Disease

MAH Conclusion

There were no cases reporting VAED/VAERD retrieved from the search of the Company global safety database. Analysis of spontaneous reports of vaccination failure did not reveal any trends suggestive of VAED/VAERD. No new safety information was identified during the reporting period for the important potential risk of VAED including VAERD.

Rapporteur assessment comment: No cases of VAED/VAERD were identified during the reporting period in the company global safety database.

Venous Thromboembolism

During this reporting period, 2,709 (1,771 medically confirmed and 938 medically unconfirmed) cases reporting VTE were identified. Of these 2,709 cases, 2,645 were serious and 64 were nonserious reporting a total of 3,726 events (3,611 serious, 115 nonserious). Of these 2,709 cases, 75 were reported from placebo-controlled studies, 36 from open-label studies, and 2,598 from post-marketing sources (including spontaneous and solicited cases).

Rapporteur assessment comment: Thromboembolism has been evaluated in depth in a specific MEA (EMEA/H/C/005737/MEA/032); as well as in the MSSRs (EMEA/H/C/005737/MEA/014.1-07). MEA 032 resulted in updates of the PI (Section 4.4 and 4.8 of the SmPC and the PIL accordingly). No new information has been provided in this PSUR; particularly since this assessment predominantly was undertaken after the DLP of the PSUR.

Immune Thrombocytopenia

The used case definition was a modified definition from the American Society of Hematology (Kelton 2018). It is acknowledged that the threshold appears very high for a case to be able to fulfil the definition of 'confirmed'. During this reporting period, 262 (217 medically confirmed and 45medically unconfirmed) cases reporting ITP were identified. Of these 262 cases, 158 were serious and 104were nonserious and reporting a total of 302 events (193 serious, 109 nonserious). Of these 262 cases, 19 were reported from placebo-controlled studies, 3 from open-label studies, and 240 from post-marketing sources (including spontaneous and solicited cases).

Table 66: Frequency of MedDRA PTs of Interest Involving the Use of Ad26.COV2.S and Reporting Immune Thrombocytopenia (Events=302)

MedDRA PTs	Number of Events	
	Serious	Nonserious
Platelet count decreased	71	16
Thrombocytopenic purpura	8	77
Thrombocytopenia	66	16
Immune thrombocytopenia	44	0
Thrombotic thrombocytopenic purpura	4	0
Total	**193**	**109**

MAH Conclusion

Based on the review of the literature (ie, Section 11), ongoing/completed clinical studies (i.e., Sections 7,

8, and 9), relevant cases retrieved from the Company global safety database, and an O/E analysis for the current reporting period, ITP is considered an important potential risk. The Company continues to monitor events of ITP and provide updated assessment when additional data becomes available.

Rapporteur assessment comment: ITP and/or thrombocytopenia has been evaluated in depth in various MSSRs (EMEA/H/C/005737/MEA/014.2-3), and in variations EMEA/H/C/005737/II/0006/G; EMEA/H/C/005737/II/020; EMEA/H/C/005737/II/0018. The case definition has also been questioned by EMA (use of Brighton collaboration definition instead of the modified one from American Society of Hematology). After the cut-off for this PSUR period, the SmPC section 4.4 was updated to include a warning regarding immune thrombocytopenia and section 4.8 includes immune thrombocytopenia as an adverse reaction with frequency unknown (II/0020).

Capillary Leak Syndrome

During this reporting period, a total of 7 medically confirmed and no medically unconfirmed cases reporting CLS were identified. These 7 cases were all serious reporting a total of 7 serious events. All 7 cases were reported from post-marketing studies (including spontaneous and solicited cases). None of the cases were reported from placebo-controlled studies or open-label studies.

Rapporteur assessment comment: CLS has been evaluated in depth in II/0010; which resulted in updates of the PI section 4.4 & 4.8 of the SmPC, PIL accordingly), and has also been reviewed in the MSSRs. No information provided in the PSUR alters previous assessments.

New Information on Other Identified Risks Not Categorised as Important

As of the DLD of this report, there was no new information on other identified risks not categorised as important associated with Ad26.COV2.S.

New Information on Other Potential Risks Not Categorised as Important

As of the DLD of this report, there were no other potential risks not categorised as important associated with Ad26.COV2.S.

2.3.3. Update on Missing Information

Use During Pregnancy

During this reporting period, 439 (154 medically confirmed and 285medically unconfirmed) cases reporting use in pregnancy/use in breastfeeding women were identified. Of these 439 cases, 78 were serious and 361 were nonserious and reported a total of 1,215 events (215 serious, 1,000 nonserious). Of these 439 cases, 44 did not meet the criteria for inclusion in this section (cases of congenital anomalies reported in patients and not related to pregnancy/lactation exposure). Additionally, 14 cases reported maternal exposure to vaccine >3 months before conception/pregnancy. These 58 cases are not discussed further. Of the remaining 381 cases, 58 were reported from placebo-controlled studies, 3 from open-label studies, and 320 from post-marketing sources (including spontaneous and solicited cases). Of these 381 cases, the most frequently reported countries of origin were the US (n=256), South Africa (n=25), and Brazil (n=22). The age range was 0.008 to 46 years. Of the 381 cases. 323 reported exposure during pregnancy, and 58 reported use in breastfeeding women.

MAH Conclusion

The review identified no trend in events related to exposure during pregnancy. Most of the cases of pregnancy were still ongoing at the time of reporting. Abnormal pregnancy outcomes represented 6.6% (25/381) of the total included cases, mainly driven by reports of spontaneous abortions (including missed and incomplete abortions) in the first trimester of pregnancy (n=12). It is estimated that 10 to 15% of recognised pregnancies result in miscarriage, and 80% of most miscarriages occur during the first trimester of pregnancy. The review of the data did not identify any evidence of an increased risk related to vaccine exposure during pregnancy. The review of cases that reported exposure via breast milk did not identify any unusual trend in the lactating mother or in exposure to children via breast milk. Most of the events experienced by vaccinated mothers were reactogenic and nonserious. The minority of lactation cases 27.6% (16/58) reported AEs in children exposed via breast milk and these were typically nonserious such as pyrexia, possibly related to concomitant infantile infection. One serious case included bloody stools; however, in this case the causality of the vaccine was confounded by the child's history of the same events prior to vaccination (bloody stools). Based on the review of the literature (i.e., Section 11), ongoing/completed clinical studies (i.e., Sections 7, 8, and 9), and relevant cases retrieved from the Company global safety database for the current reporting period, no new safety information was identified during the reporting period for the missing information of use during pregnancy and use in breastfeeding women.

Rapporteur assessment comment: It can be agreed with the MAH that during this reporting period no new safety concern is detected here. However, experience is still limited to draw conclusions regarding safety following vaccination of pregnant women.

Use in Immunocompromised Patients

During this reporting period, 4,491 (1,639 medically confirmed and 2,852 medically unconfirmed) cases reporting use in immunocompromised patients were identified. Of these 4,491 cases, 1,956 were serious and 2,535 were nonserious reporting a total of 26,377 events (8,671 serious, 17,706 nonserious).
Of these 4,491 cases, 205 were reported from placebo-controlled studies, 93 from open-label studies, and 4,193 from post-marketing sources (including spontaneous and solicited cases).

Table 76: Frequency of the Top 10 MedDRA PTs Involving the Use of Ad26.COV2.S and Reporting Use in Immunocompromised Patients (Events=26,377)

MedDRA PTs[a]	Number of Events	
	Serious	Nonserious
Headache	170	1,241
Fatigue	107	1,012
Pyrexia	110	880
Chills	68	754
Nausea	84	569
Pain	62	579
Pain in extremity	98	537
Myalgia	47	490
Dizziness	82	406
Injection site pain	18	449

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term.
a: The most frequently reported 10 MedDRA PTs have been presented.

MAH Conclusion

Review of the literature (i.e., Section 11), ongoing/completed clinical studies (i.e., Sections 7, 8, and 9), and relevant cases retrieved from the Company global safety database for the current reporting period, showed that the safety profile of Ad26.COV2.S. in immunocompromised patients is consistent with the known profile of the vaccine overall. The most frequently reported events represented reactogenicity and included events of headache, fatigue, and pyrexia. No new safety concern with the use of Ad26.COV2.S. in immunocompromised patients was identified.

Rapporteur assessment comment: It can be agreed that during the reporting period the safety profile in immunocompromised subjects appears to be in line with the known safety profile of the vaccine overall.

Use in Patients with Autoimmune or Inflammatory Disorders

During this reporting period, 2,229 (977 medically confirmed and 1,252 medically unconfirmed) cases reporting use in patients with autoimmune or inflammatory disorders were identified. Of these 2,229 cases, 1,189 were serious and 1,040 were nonserious reporting a total of 12,209 events (4,921 serious, 7,288 nonserious). Of these 2,229 cases, 164 were reported from placebo-controlled studies, 100 from open-label studies, and 1,965from post-marketing sources (including spontaneous and solicited cases).

Table 79: Frequency of the Top 10 MedDRA PTs Involving the Use of Ad26.COV2.S and Reporting Use in Patients With Autoimmune or Inflammatory Disorders (Events=12,209)

MedDRA PTs[a]	Number of Events	
	Serious	Nonserious
Headache	82	442
Fatigue	48	406
Pyrexia	53	312
Pain in extremity	48	254
Pain	32	263
Chills	26	250
Nausea	38	190
Arthralgia	25	188
Myalgia	25	172
Dizziness	41	149

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term.

a: The most frequently reported 10 MedDRA PTs have been presented.

MAH Conclusion

Review of the literature (i.e., Section 11), ongoing/completed clinical studies (i.e., Sections 7, 8, and 9), and relevant cases retrieved from the Company global safety database for the current reporting period showed that the safety profile of Ad26.COV2.S. in patients with underlying autoimmune or inflammatory disorders is consistent with the known profile of the vaccine overall. The most frequently reported events represented reactogenicity and included events of headache, fatigue, and pyrexia. No new safety concern with the use of Ad26.COV2.S. in patients with autoimmune or inflammatory disorders was identified.

Rapporteur assessment comment:

An in-depth review regarding flare of autoimmune diseases is provided above. No additional points are raised based on the data presented by the MAH in this section.

Use in Frail Patients with Comorbidities (eg, Chronic Obstructive Pulmonary Disease, Diabetes, Chronic Neurological Disease, Cardiovascular Disorders)

During this reporting period, 73 (33 medically confirmed and 40 medically unconfirmed) cases reporting use in frail patients with comorbidities were identified. Of these 73 cases, 37 were serious and 36 were nonserious reporting a total of 282 events (116 serious, 166 nonserious). Of these 73 cases, 14 were reported from placebo-controlled studies, 4 from open-label studies, and 55 from post-marketing sources (including spontaneous and solicited cases).

Table 82: Frequency of MedDRA PTs Involving the Use of Ad26.COV2.S and Reporting Use In Frail Patients With Comorbidities (eg, Chronic Obstructive Pulmonary Disease, Diabetes, Chronic Neurological Disease, Cardiovascular Disorders) (Events=282)

MedDRA PTs	Number of Events[a]	
	Serious	Nonserious
Headache	1	14
Fatigue	1	10
Deep vein thrombosis	9	0
Chills	0	9
Pain in extremity	2	6
Pyrexia	1	7
Pain	1	5
Injection site pain	0	6
Cerebrovascular accident	5	0
Nausea	0	5
Thrombocytopenia	3	2
Arthralgia	1	4
Chest pain	2	2
Insomnia	0	4
Pulmonary embolism	4	0
Thrombosis	4	0

Key: COVID-19=Coronavirus Disease-2019; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term.
a: Events reported ≥4 are presented.

Placebo-controlled studies During this reporting period, 14 cases reporting use in frail patients with comorbidities were retrieved from placebo-controlled studies. Of these 14 cases, 8 were from VAC31518COV3009 and 6 from VAC31518COV3001. These 14 cases reported 20 events (12 serious, 8 nonserious), the most frequently reported country of origin was the US (n=5). The age range was 36 to 72 years, and 8 concerned females and 6 males. The events reported included 2 each of chest pain, deep vein thrombosis, platelet count decreased, and thrombocytopenia, and 1 each of anaemia, cerebral thrombosis, cerebrovascular accident, coronary artery stenosis, dyspnoea, iron deficiency, muscle spasms, osteoarthritis, pancreatitis necrotising, petechiae, pulmonary embolism, and splenic vein thrombosis. The mean and median TTO was 70.6 days and 86 days, respectively. Where reported (n=19), the outcome was resolved (n=7), not resolved (n=5), resolving (n=4), and resolved with sequelae (n=3). In 18 events, the Company/reporter causality was assessed as not related and in 2 events the Company causality was assessed as not related and reporter causality was assessed as related.

Open-label studies (Sisonke and Brazil Early Access). During this reporting period, 4 cases reporting use in frail patients with comorbidities were retrieved from open-label studies. All 4 cases were from VAC31518COV3012 (Sisonke), and reported 4 serious events, all and concerned females. The age range was 29 to 52 years. The events reported included deep vein thrombosis (n=2), and 1 each of cerebrovascular accident, and venous thrombosis. The mean and median TTO was 19.2 days and 20.5 days, respectively. The event outcomes were reported as resolving (n=3), and not resolved (n=1). In 2 events, the Company/reporter causality assessed as not related. In 1 event, the Company causality assessed as not related with reporter assessed as possibly related and, 1 event the Company causality assessed as not related with the reporter causality assessed as related.

MAH Conclusion

Review of the available data, showed that the safety profile of Ad26.COV2.S in frail patients with comorbidities is consistent with the known profile of the vaccine in the overall Ad26.COV2.S vaccinated population. The most frequently reported events represented reactogenicity (e.g. headache, fatigue, and pyrexia). No new safety concern with the use of Ad26.COV2.S. in patients with comorbidities (eg, COPD, diabetes, chronic neurological disease, cardiovascular disorders) was identified.

Rapporteur assessment comment: It can be agreed that during the reporting period the safety profile in patients with comorbidities (eg, chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders) appears to be in line with the known safety profile of the vaccine overall.

Interaction with Other Vaccines

During this reporting period, 51 (22 medically confirmed and 29 medically unconfirmed) cases reporting the use with concomitant vaccination were identified. Of the 51 cases, 25were serious and 26 nonserious reporting a total of 248 events (75serious, 173 nonserious). Most of the events reported in subjects receiving Ad26.COV2.S with concomitant vaccines were reactogenic and/or listed for Ad26.COV2.S. No abnormal trend in events was observed. Based on review of all the available data, no safety concerns have been identified for use with concomitant vaccines during the reporting period.

Rapporteur assessment comment: Agreed.

Long-term Safety

Information on long-term safety is not available at this time.

2.3.4. Adverse Events of Special Interest

2.3.4.1. Cardiac Disorders

Arrhythmia

During this reporting period, 222 (90 medically confirmed and 132 medically unconfirmed) cases reporting arrhythmia were identified. Of these 222 cases, 181 were serious and 41 were nonserious reporting a total of 241 events (182 serious, 59 nonserious). Of these 222 cases, 22 were reported from placebo-controlled studies and 200 from post-marketing sources (including spontaneous and solicited cases). None of the cases were reported from open-label studies.

Table 85: Frequency of MedDRA PTs of Interest Involving the Use of Ad26.COV2.S and Reporting Arrhythmia (Events=241)

MedDRA PTs	Number of Events	
	Serious	Nonserious
Atrial fibrillation	70	1
Arrhythmia	46	0
Heart rate irregular	5	32
Extrasystoles	1	11
Ventricular extrasystoles	3	8
Sinus tachycardia	5	5
Pulseless electrical activity	6	0
Cardiac flutter	6	0
Atrial flutter	5	1
Ventricular fibrillation	6	0
Supraventricular tachycardia	5	0
Ventricular tachycardia	5	0
Bundle branch block right	4	0
Atrioventricular block	3	0
Supraventricular extrasystoles	1	1
Atrioventricular block complete	2	0
Atrioventricular block second degree	2	0
Atrioventricular block first degree	1	0
Ventricular arrhythmia	1	0
Ventricular tachyarrhythmia	1	0
Arrhythmia supraventricular	1	0
Bundle branch block left	1	0
Electrocardiogram repolarisation abnormality	1	0
Electrocardiogram QT prolonged	1	0
Total	**182**	**59**

Key: MedDRA=Medical Dictionary for Regulatory Activities;; PT=Preferred Term.

Table 86: Broad O/E and Sensitivity Analysis Results (Arrythmia)

Region	Broad O/E Analysis				Sensitivity Analysis	
	Age Range (Years)	Observed Count[a]	O/E Ratio (95% CI)[b] (PE, 100% RP)		O/E Ratio (95% CI)[b] (LB, 50% RP)	
US	18 to 59	45.43	0.057	(0.042-0.076)	0.114	(0.083-0.152)
	≥60	43.45	0.019	(0.014-0.025)	0.038	(0.027-0.051)
EU	18 to 59	55.46	0.038	(0.029-0.049)	0.079	(0.060-0.103)
	≥60	14.48	0.006	(0.003-0.010)	0.012	(0.007-0.020)

Key: CI=Confidence Interval; EU=European Union; LB=Lower Bound; O/E=Observed versus Expected; PE=Point Estimate; RP=Reporting Percentage; US=United States.

a: Counts included cases with events of interest that occurred within the risk window, and cases where time-to-onset was 0 or not reported.

b: Poisson exact confidence interval (95% CI).

MAH Conclusion

Based on the review of the literature (i.e., Section 11), ongoing/completed clinical studies (i.e., Sections 7, 8, and 9), relevant cases retrieved from the Company global safety database, and an O/E analysis for

the current reporting period, no new safety information was identified regarding arrythmia. An assessment of aggregate data and O/E analysis did not highlight a safety concern.

Rapporteur assessment comment: No new safety concern regarding arrythmia is detected.

Cardiac Inflammatory Disorders, Including Myocarditis and Pericarditis

MAH Conclusion: A cumulative review was conducted and included in the August MSSR. Based on this review of non-clinical studies, clinical trial data, post-marketing surveillance data and a review of the literature, myocarditis/pericarditis is not considered associated with the use of Ad26.COV2.S. Key factors supporting this conclusion include:

- Lack of literature reports describing myocarditis/pericarditis with respect to adenoviral vaccines and lack of evidence as no sentinel cases were identified
- Disproportionality in the O/E analysis is limited mainly to males in the age group of 18 to 29 years, with limitations that overall lower numbers of Janssen Ad26.COV2.S vaccine doses are administered as compared to that of mRNA COVID-19 vaccines or ChAdOx1 COVID-19 vaccine and myocarditis signal with mRNA vaccines may cause stimulated reporting.
- The observed rates are lower than those seen with mRNA COVID-19 vaccines and are in line with the background incidence rates observed in the general population. The rates for comparison have not taken into consideration the population that has been exposed to COVID-19 virus either with symptomatic or asymptomatic infection, in which rates can be expected to be higher than those used for comparison based on historical data.
- The biological mechanisms behind immunogenic phenomena by mRNA vaccines and adenoviral vaccines are obviously different as they involve mutually exclusive bioactive components, thus myocarditis/pericarditis seen so far in the post-marketing experience with mRNA COVID-19 vaccines is not considered to be a risk for Ad26.COV2.S based on this analysis.

Rapporteur assessment comment:

These items have been assessed in depth in the MSSRs, including cumulative reviews. At this stage, there is currently insufficient data to support a causal relationship with the COVID-19 vaccine Janssen and myocarditis or pericarditis. Nevertheless, pericarditis and myocarditis should be closely monitored for the coming MSSRs and PSURs.

Cardiomyopathy

During this reporting period, 23 (18 medically confirmed and 5 medically unconfirmed) cases reporting cardiomyopathy were identified. All 23 cases were serious reporting a total of 27 events (26 serious, 1 nonserious). All of these cases were reported from post-marketing sources (including spontaneous and solicited cases). None of the cases were reported from placebo-controlled studies or open-label studies.

Table 92: Frequency of MedDRA PTs of Interest Involving the Use of Ad26.COV2.S and Reporting Cardiomyopathy (Events=27)

MedDRA PTs	Number of Events	
	Serious	Nonserious
Ejection fraction decreased	10	1
Cardiomyopathy	7	0
Myocardial fibrosis	2	0
Ischaemic cardiomyopathy	2	0
Congestive cardiomyopathy	2	0
Stress cardiomyopathy	2	0
Cardiac hypertrophy	1	0
Total	**26**	**1**

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term.

Table 93: Broad O/E and Sensitivity Analysis Results (Cardiomyopathies)

Region	Broad O/E Analysis				Sensitivity Analysis	
	Age Range (Years)	Observed Count[a]	O/E Ratio (95% CI)[b] (PE, 100% RP)		O/E Ratio (95% CI)[b] (LB, 50% RP)	
US	18 to 59	9.00	**2.744**	**(1.255, 5.209)**	**5.633**	**(2.576, 10.693)**
	≥60	6.00	0.624	(0.229, 1.358)	**2.106**	**(0.773, 4.583)**
EU	18 to 59	2.00	0.650	(0.079-2.350)	**1.335**	**(0.162-4.823)**
	≥60	1.00	0.128	(0.003-0.714)	0.433	(0.011-2.410)

Key: CI=Confidence Interval; EU=European Union; LB=Lower Bound; O/E=Observed versus Expected; PE=Point Estimate; RP=Reporting Percentage; US=United States.
a: Counts included cases with events of interest that occurred within the risk window, and cases where time-to-onset was 0 or not reported.
b: Poisson exact confidence interval (95% CI).

Table 94: Restricted O/E and Sensitivity Analysis Results (Cardiomyopathies)

Region	Restricted O/E Analysis				Sensitivity Analysis	
	Age Range (Years)	Observed Count[a]	O/E Ratio (95% CI)[b] (PE, 100% RP)		O/E Ratio (95% CI)[b] (LB, 50% RP)	
US	18 to 59	8.00	2.439	**(1.053, 4.806)**	**5.007**	**(2.162, 9.866)**
	≥60	5.00	0.520	(0.169, 1.213)	**1.755**	**(0.570, 4.095)**
EU	18 to 59	1.00	0.325	(0.008-1.812)	0.668	(0.017-3.720)

Key: CI=Confidence Interval; EU=European Union; LB=Lower Bound; O/E=Observed versus Expected; PE=Point Estimate; RP=Reporting Percentage; US=United States.
a: Counts included cases with events of interest that occurred within the risk window only.
b: Poisson exact confidence interval (95% CI).

MAH Conclusion

Based on the review of the literature (i.e., Section 11), ongoing/completed clinical studies (ie, Sections 7, 8, and 9), relevant cases retrieved from the Company global safety database, and an O/E analysis for the current reporting period, no new safety information was identified during the reporting period for cardiomyopathy.

Rapporteur assessment comment: No new safety concern detected here.

Coronary Artery Disease, Including Acute Myocardial Infarction

During this reporting period, 345(233 medically confirmed and 112 medically unconfirmed) cases reporting CAD, including acute myocardial infarction were identified. Of these 345 cases, 343 were serious and 2 were nonserious reporting a total of 445 events (441 serious, 4 nonserious). Of these 345 cases, 54 were reported from placebo-controlled studies, 3 from open-label studies, and 288 from post-marketing sources (including spontaneous and solicited cases).

Table 96: Frequency of MedDRA PTs of Interest Involving the Use of Ad26.COV2.S and Reporting Coronary Artery Disease, Including Acute Myocardial Infarction (Events=445)

MedDRA PTs	Number of Events	
	Serious	Nonserious
Myocardial infarction	138	0
Acute myocardial infarction	81	0
Troponin increased	45	2
Angina pectoris	40	1
Coronary artery occlusion	21	0
Coronary artery disease	20	1
Coronary arterial stent insertion	19	0
Coronary artery thrombosis	15	0
Acute coronary syndrome	8	0
Myocardial ischaemia	7	0
Troponin I increased	6	0
Coronary artery stenosis	6	0
Percutaneous coronary intervention	5	0
Angina unstable	5	0
Coronary artery bypass	4	0
Coronary angioplasty	4	0
Arteriosclerosis coronary artery	3	0
Stress cardiomyopathy	2	0
Arteriospasm coronary	2	0
Coronary artery embolism	2	0
Blood creatine phosphokinase MB increased	2	0
Ischaemic cardiomyopathy	2	0
Microvascular coronary artery disease	1	0
ECG signs of myocardial ischaemia	1	0
Cardiac perfusion defect	1	0
Coronary artery dissection	1	0
Total	**441**	**4**

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term.

Table 97: Broad O/E and Sensitivity Analysis Results [Coronary Artery Disease (Including Acute Myocardial Infarction)]

Region	Broad O/E Analysis				Sensitivity Analysis	
	Age Range (Years)	Observed Count[a]	O/E Ratio (95% CI)[b] (PE, 100% RP)		O/E Ratio (95% CI)[b] (LB, 50% RP)	
US	18 to 59	89.58	0.183	(0.147, 0.225)	0.398	(0.320, 0.489)
	≥60	93.21	0.094	(0.076, 0.115)	0.198	(0.160, 0.243)
EU	18 to 59	52.59	0.114	(0.085-0.149)	0.247	(0.185-0.324)
	≥60	22.36	0.028	(0.017-0.042)	0.058	(0.037-0.088)

Key: CI=Confidence Interval; EU=European Union; LB=Lower Bound; O/E=Observed versus Expected; PE=Point Estimate; RP=Reporting Percentage; US=United States.
a: Counts included cases with events of interest that occurred within the risk window, and cases where time-to-onset was 0 or not reported.
b: Poisson exact confidence interval (95% CI).

MAH Conclusion

Based on the review of the literature (ie, Section 11), ongoing/completed clinical studies (ie, Sections 7, 8, and 9), relevant cases retrieved from the Company global safety database, and an O/E analysis for the current reporting period, no new safety information was identified during the reporting period for CAD.

Rapporteur assessment comment: No new safety concern is detected here.

Heart Failure

During this reporting period, 86 (66 medically confirmed cases and 20 medically unconfirmed) cases reporting heart failure were identified. All 86 cases were serious and reported a total of 99 events (98 serious, 1 nonserious). Of these 86 cases, 10 were reported from placebo-controlled studies, 2 from open-label studies, and 74 from post-marketing sources (including spontaneous and solicited cases).

Table 99: Frequency of MedDRA PTs of Interest Involving the Use of Ad26.COV2.S and Reporting Heart Failure (Events=99)

MedDRA PTs	Number of Events	
	Serious	Nonserious
Cardiac failure	25	0
Cardiac failure congestive	20	0
Pulmonary oedema	17	0
Ejection fraction decreased	10	1
Cardiogenic shock	5	0
Cor pulmonale acute	4	0
Cor pulmonale	4	0
Right ventricular failure	3	0
Acute left ventricular failure	3	0
Left ventricular failure	2	0
Cardiac failure acute	2	0
Obstructive shock	1	0
Acute pulmonary oedema	1	0
Cardiac failure chronic	1	0
Total	**98**	**1**

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term.

Table 100: Broad O/E and Sensitivity Analysis Results (Heart Failure)

Region	Broad O/E Analysis				Sensitivity Analysis	
	Age Range (Years)	Observed Count[a]	O/E Ratio (95% CI)[b] (PE, 100% RP)		O/E Ratio (95% CI)[b] (LB, 50% RP)	
US	18 to 59	27.93	0.102	(0.068-0.148)	0.332	(0.221-0.480)
	≥60	22.03	0.004	(0.003-0.006)	0.008	(0.005-0.012)
EU	18 to 59	1.00	0.005	(0.000-0.030)	0.012	(0.000-0.068)
	≥60	8.00	0.003	(0.001-0.005)	0.006	(0.002-0.011)

Key: CI=Confidence Interval; EU=European Union; LB=Lower Bound; O/E=Observed versus Expected; PE=Point Estimate; RP=Reporting Percentage; US=United States.
a: Counts included cases with events of interest that occurred within the risk window, and cases where time-to-onset was 0 or not reported.
b: Poisson exact confidence interval (95% CI).

MAH Conclusion

Based on the review of the literature (ie, Section 11), ongoing/completed clinical studies (ie, Sections 7, 8, and 9), relevant cases retrieved from the Company global safety database, and an O/E analysis for the

current reporting period, no new safety information was identified during the reporting period for heart failure.

Rapporteur assessment comment: No new safety concern is detected here.

2.3.4.2. Immune System Disorders

Autoimmune Thyroiditis

Although the PBRER reporting period is from 25 February 2021 to 24 August 2021, the O/E analysis covers the period of 25 February 2021 to 31 August 2021. A broad O/E analysis with sensitivity analysis was performed for the US and EU, stratified by age groups: 18 to 59, ≥60 years old. If the O/E ratio was >1 in the sensitivity analysis, a restricted analysis was performed for the respective region and age-group.

Results/Discussion

During this reporting period, 20 (7 medically confirmed and 13 medically unconfirmed) cases reporting autoimmune thyroiditis were identified. Of these 20 cases, 17 were serious and 3 were nonserious reporting a total of 21 events (16 serious, 5 nonserious). All of the cases were reported from post-marketing sources (including spontaneous and solicited cases). None of these cases were reported from placebo-controlled studies or open-label studies. The frequency distribution of the 21 MedDRA PTs of interest reported in these 20 cases is presented in Table 102 below. A single case may contain more than 1 EOI search strategy).

Table 102: Frequency of MedDRA PTs of Interest Involving the Use of Ad26.COV2.S and Reporting Autoimmune Thyroiditis (Events=21)

MedDRA PTs	Number of Events	
	Serious	Nonserious
Basedow's disease	8	0
Autoimmune thyroiditis	5	0
Thyroiditis	0	5
Addison's disease	1	0
Thyroiditis subacute	1	0
Thyroiditis acute	1	0
Total	**16**	**5**

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term.

Out of the 20 cases, 8 reported a pre-existing thyroid disorder in the patients' medical history. TTO, where provided (n=7) ranged from 0 to 59 days (median=12 days). None of these cases reported thyroid replacement therapy for the event, treatment medications were not reported in the majority of these cases (n=6). In the remaining 2 cases, treatment of the event included surgery for thyroid nodule removal or steroids (patients pre-existing steroid medication doses for Addison's disease were increased and the event resolved). In 5 out of the 20 cases the patient did not have a history of thyroid disorder and the EOI was considered new onset. TTO ranged from 7 to 84 days (median=44 days). Treatment details were not reported in 3 cases. In the remaining 2 cases, methimazole was used and the events were reported as not resolved. None of these cases reported the patient was needing thyroid replacement therapy for the event. In the remaining 7 cases, it was not possible to determine whether the reported EOI was new onset or aggravation of pre-existing disease, as no information was reported with regards to the patients' medical history. TTO, where reported (n=6) ranged from 0 to 75 days (median=5 days). There was no information reported the patients needing thyroid replacement therapy or any other treatment medication for the event. Individual case safety report (ICSR) literature cases received during the reporting period were reviewed. There were no literature ICSR identified. Review of the cases,

including demographics, concomitant medications, concurrent conditions/medical history, outcome, and seriousness received during this reporting period did not identify evidence suggestive of autoimmune thyroiditis being causally associated with Ad26.COV2.S.

O/E Analysis Results

Results of the broad O/E and sensitivity analysis are presented in Table 103.

Table 103: Broad O/E and Sensitivity Analysis Results (Autoimmune Thyroiditis)

Broad O/E Analysis					Sensitivity Analysis	
Region	Age Range (Years)	Observed Count[a]	O/E Ratio (95% CI)[b] (PE, 100% RP)		O/E Ratio (95% CI)[b] (LB, 50% RP)	
US	18 to 59	13.64	0.018	(0.010, 0.030)	0.107	(0.058, 0.180)
	≥60	2.34	0.003	(0.000, 0.010)	0.014	(0.002, 0.047)
EU	18 to 59	5.93	0.015	(0.005, 0.033)	0.089	(0.032, 0.195)
	≥60	0.06	0.000	(0.000, 0.010)	0.001	(0.000, 0.049)

Key: CI=Confidence Interval; EU=European Union; LB=Lower Bound; O/E=Observed versus Expected; PE=Point Estimate; RP=Reporting Percentage; US=United States.
a: Counts included cases with events of interest that occurred within the risk window, and cases where time-to-onset was 0 or not reported.
b: Poisson exact confidence interval (95% CI).

MAHs Conclusion Based on the review of the literature, ongoing/completed clinical studies, relevant cases retrieved from the Company global safety database, and an O/E analysis for the current reporting period, at present, there is insufficient evidence to establish a causal association between Ad26.COV2.S and autoimmune thyroiditis. MAH proposes to continue monitoring this topic via routine PV activities.

Rapporteur assessment comment: No new safety concern is detected here.

Type 1 Diabetes Mellitus

During this reporting period, 19 (10 medically confirmed and 9 medically unconfirmed) cases reporting type 1 diabetes mellitus were identified. All of the 19 cases were serious and reported a total of 19 serious events. Of these 19 cases, 1 was reported from placebo-controlled studies study, 1 was from open-label study, and 17 were from post-marketing sources (including spontaneous and solicited cases).

O/E Analysis Results

Results of the broad O/E and sensitivity analysis are presented in Table 106.

Table 106: Broad O/E and Sensitivity Analysis Results (Type 1 Diabetes Mellitus)

O/E Analysis Results					Sensitivity Analysis	
Region	Age Range (Years)	Observed Count[a]	O/E Ratio (95% CI)[b] (PE, 100% RP)		O/E Ratio (95% CI)[b] (LB, 50% RP)	
US	18 to 59	10.64	0.013	(0.007-0.024)	0.027	(0.013-0.049)
	≥60	1.34	0.002	(0.000-0.009)	0.004	(0.000-0.017)
EU	18 to 59	1.93	0.005	(0.001-0.017)	0.011	(0.001-0.040)
	≥60	0.06	0.000	(0.000-0.024)	0.001	(0.000-0.058)

Key: CI=Confidence Interval; EU=European Union; LB=Lower Bound; O/E=Observed versus Expected; PE=Point Estimate; RP=Reporting Percentage; US=United States.
a: Counts included cases with events of interest that occurred within the risk window-and cases where time-to-onset was 0 or not reported.
b: Poisson exact confidence interval (95% CI).

A review of the results for the US and EU broad analysis (applying a 100% reporting percentage and point estimate incident rate) and the sensitivity analysis (applying a 50% reporting percentage and lower bound incident rate) showed an O/E ratio of <1 in the US and EU for both age groups. A restricted O/E with sensitivity analysis was not required.

MAHs Conclusion

Based on the review of the literature (i.e., Section 11), ongoing/completed clinical studies (ie, Sections 7, 8, and 9), relevant cases retrieved from the Company global safety database, and an O/E analysis for the

current reporting period, no new safety information was identified during the reporting period for type 1 diabetes mellitus.

Rapporteur assessment comment: No new safety concern is detected here.

2.3.4.3. Musculoskeletal Disorders

Acute Aseptic Arthritis

Although the PBRER reporting period is from 25 February 2021 to 24 August 2021, the O/E analysis covers the period of 25 February 2021 to 31 August 2021.

Results/Discussion

During this reporting period, 264(184 medically confirmed and 80 medically unconfirmed) cases reporting acute aseptic arthritis were identified. Of these, 96 were serious and 168 were nonserious reporting a total of 271 events (80 serious, 191 nonserious). Nineteen were from placebo-controlled studies, 2 from open-label studies, and 243 from post-marketing sources. See Table 108. A single case may contain more than 1 EOI.

Table 108: Frequency of MedDRA PTs of Interest Involving the Use of Ad26.COV2.S and Reporting Acute Aseptic Arthritis (Events=271)

MedDRA PTs	Number of Events	
	Serious	Nonserious
Arthritis	11	162
Rheumatoid arthritis	27	0
Osteoarthritis	15	4
Gout	2	10
Periarthritis	3	7
Spinal osteoarthritis	6	0
Temporomandibular joint syndrome	0	3
Arthritis reactive	3	0
Still's disease	3	0
Facet joint syndrome	3	0
Rheumatic disorder	0	2
Acute aseptic arthritis	2	0
Polyarthritis	2	0
Synovitis	1	0
Traumatic arthritis	0	1
Arthritis infective	1	0
Spondylitis	0	1
Axial spondylarthritis	0	1
Rheumatic fever	1	0
Total	**80**	**191**

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term.

Placebo-controlled Studies

During this reporting period, 19 cases reporting acute aseptic arthritis were retrieved from placebo-controlled studies. Of these 19 cases, 10 were reported from VAC31518COV3009, 8 were from VAC31518COV3001, and 1 from VAC31518COV1001. There were 17 serious, 2 nonserious events. The most frequently reported country of origin was the US (n=12); 10 concerned males and 9 females with an age range of 30 to 76 years.

The EOI included osteoarthritis (n=15), spinal osteoarthritis (n=2), traumatic arthritis (n=1), and arthritis infective (n=1). The mean and median TTO was 97.5 days and 83 days, respectively. The outcome for the 19 events were reported as resolved (n=14), not resolved (n=3) and resolving (n=2). EOI causality was reported as: Company/reporter assessed as not related (n=19).

Open-label Studies (VAC31518COV3012 [Sisonke]; and VA C31518COV4007 [Brazil Early Access])

During this reporting period, 2 cases reporting acute aseptic arthritis from open-label studies were identified. These 2 cases were reported from VAC31518COV3012 (Sisonke) reporting the same serious EOI of arthritis reactive. These 2 cases were reported from South Africa. One case concerned a 30-year-old male, and the other a 34-year-old female. The mean and median TTO were 8.5 days. The outcomes for the 2 EOI were reported as resolved (n=1) and resolving (n=1). EOI causality was reported as: Company/reporter assessed as not related, and in the second case the reporter causality was considered related; however, the Company assessed the event of acute aseptic arthritis as not related because of the patient recent history of COVID-19 infection which likely triggered the event.

Post-marketing Sources (Including Spontaneous and Solicited Cases)

During this reporting period, 243 cases reporting acute aseptic arthritis from post-marketing sources were identified. These 243 cases reported 250 EOIs (61 serious, 189 nonserious). Of these 243 cases, the most frequently reported country of origin was Korea, Republic of (n=124). Of the 243 cases, 125 concerned males, 106 females, and 12 had no sex reported. The age range was 19 to 84 years.

The EOI (n≥2) included arthritis (n=173), rheumatoid arthritis (n=27), gout (n=12), periarthritis (n=10), osteoarthritis and spinal osteoarthritis (n=4 each), 3 each of temporomandibular joint syndrome, facet joint syndrome, Still's disease, and 2 each of acute aseptic arthritis, polyarthritis, and rheumatic disorder. The mean and median TTO was 6.4 days and 2 days, respectively. Where reported (n=118), the outcomes were reported as not resolved (n=62), resolved (n=38), resolving (n=17), and resolved with sequelae (n=1).

Two fatal cases were reported during the interval that included the nonserious EOIs of arthritis and spondylitis, respectively. One case was reported from the French National Agency Medicines & Health Safety on multiple events in multiple unidentifiable patients after receiving Ad26.COV2.S., and no individual case details were provided; therefore, this case could not be assessed for the causality of the vaccine. The other case was from social media (news article) that concerned a 31-year-old male from Korea. This case had a traumatic aetiology as 22 days post-vaccination, the patient experienced a fall, and an unspecified duration later died of multiple fractures and haemorrhage. An autopsy was performed but the results were not available at the time of the report.

O/E Analysis

Results of the broad O/E and sensitivity analysis are presented in Table 109.

Table 109: Broad O/E Analysis Results (Acute Aseptic Arthritis)

	O/E Analysis				Sensitivity Analysis	
Region	Age Range (Years)	Observed Count[a]	O/E Ratio (95% CI)[b] (PE, 100% RP)		O/E Ratio (95% CI)[b] (LB, 50% RP)	
US	18 to 59	49.00	0.131	(0.097-0.173)	0.313	(0.232-0.414)
	≥60	42.83	0.289	(0.209-0.389)	0.693	(0.501-0.934)
EU	18 to 59	19.73	0.005	(0.003-0.008)	0.011	(0.007-0.017)
	≥60	9.24	0.002	(0.001-0.004)	0.005	(0.002-0.009)

Key: CI=Confidence Interval; EU=European Union; LB=Lower Bound; O/E=Observed versus Expected; PE=Point Estimate; RP=Reporting Percentage; US=United States.
a: Counts included cases with events of interest that occurred within the risk window, and cases where time-to-onset was 0 or not reported.
b: Poisson exact confidence interval (95% CI).

A review of the results for the US and EU broad analysis (applying a 100% reporting percentage and point estimate incident rate) and the sensitivity analysis (applying a 50% reporting percentage and lower bound incident rate) showed an O/E ratio of <1 in the US and EU for both age groups. A restricted O/E analysis was not required.

MAHs Conclusion Based on the review available data, none of the cases met the case definition. Most of the events were nonserious and reported most of the arthritis which were likely related to arthralgia considered as a reactogenic event. There was no evidence suggestive that acute aseptic arthritis is associated with the use of Ad.26.COV2.S.

Rapporteur assessment comment: No new safety concern is detected here.

2.3.4.4. Nervous System Disorders

Bell's Palsy

Although the PBRER reporting period is from 25 February 2021 to 24 August 2021, the O/E analysis covers the period of 25 February 2021 to 31 August 2021.

Results/Discussion

During this reporting period, 218 (120 medically confirmed and 98 medically unconfirmed) cases reporting Bell's palsy were identified; 213 serious and 5 were nonserious reporting a total of 241 events (231 serious, 10 nonserious). Three were from placebo-controlled studies, 7 were from open-label studies, and 208 were from post-marketing sources. See Table 111 below.

Table 111: Frequency of MedDRA PTs of Interest Involving the Use of Ad26.CoV2.S and Reporting Bell's Palsy (Events=241)

MedDRA PTs	Number of Events	
	Serious	Nonserious
Facial paralysis	132	0
Bell's palsy	64	0
Facial paresis	35	9
Facial nerve disorder	0	1
Total	**231**	**10**

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term.

Placebo-controlled Studies

During this reporting period, 3 cases reporting Bell's palsy were retrieved from placebo-controlled studies (all serious). Two were from VAC31518COV3001, and 1 from VAC31518COV3009; from Brazil, the US and Belgium. One concerned a female and 2 males with an age range of 37 to 62 years: Bell's palsy (n=2) and facial paresis (n=1). The mean and median TTO was 27.7 days and 15days, respectively. The outcome for the 3 events of interest was reported as resolving (n=1) and resolved (n=2). Company causality was assessed as not related; however, the reporter causality was assessed as related for these 3 cases.

Open-label Studies [VAC31518COV3012 (Sisonke); and VAC31518COV4007 (Brazil Early Access)]

During this reporting period, 7 cases reporting Bell's palsy were retrieved from open-label studies. These 7 cases reported 7 serious EOIs. All 7 cases were reported from VAC31518COV3012 (Sisonke); 5 concerned females and 2 males with an age range of 36 to 77 years. The EOI included Bell's palsy in all of the cases. The mean and median TTO was 11.9 days and 6 days, respectively. The outcome for the 7 events was reported as resolving (n=5) and not resolved (n=2). EOI causality was reported as: Company assessed as not related with reporter assessed as related (n=4); Company assessed as not related with reporter causality not reported (n=2); and Company/reporter assessed as not related (n=1).

Post-marketing Sources (Including Spontaneous and Solicited Cases)

During this reporting period, 208 cases reporting Bell's palsy were retrieved from post-marketing sources; corresponding to 231 EOIs (221 serious, 10 nonserious), and most frequently from the US (n=133). Of the 208 cases, 115 concerned males, 87 females, and 6 did not report sex. The age range was 18 to 89 years. The EOIs included facial paralysis (n=132), Bell's palsy (n=55), facial paresis (n=43), and facial nerve disorder (n=1). The mean and median TTO was 18.3 days and 14days, respectively. Where reported (n=183), the outcome was reported as not resolved (n=130), resolving

(n=27), resolved (n=25), and fatal (n=1). The fatal EOI reported in 1 case was facial paralysis. Individual case safety report (ICSR) literature cases received during the reporting period were reviewed and no information was identified that would change the characterization of Bell´s palsy. During the reporting period, 1 literature case was received concerning a 62-year-old female who experienced Bell´s palsy. Relevant medical history included diabetes mellitus and hypertension. The TTO and outcome of Bell´s palsy was not reported. Review of the cases, including demographics, outcome, and seriousness received during this reporting period did not identify evidence that would support Bell's palsy is causally associated with Ad26.COV2.S.

O/E Analysis

Results of the broad O/E and sensitivity analysis are presented in Table 112.

Table 112: Broad O/E Analysis Results (Bell's Palsy)

	O/E Analysis				Sensitivity Analysis	
Region	Age Range (Years)	Observed Count[a]	O/E ratio (95% CI)[b] (PE, 100% RP)		O/E ratio (95% CI)[b] (LB, 50% RP)	
US	18 to 59	80.43	0.066	(0.052-0.082)	0.154	(0.122-0.192)
	≥60	41.45	0.057	(0.041-0.077)	0.114	(0.082-0.154)
EU	18 to 59	54.73	0.182	(0.137-0.238)	0.371	(0.279, 0.483)
	≥60	10.24	0.100	(0.049-0.183)	0.205	(0.100, 0.375)

Key: CI=Confidence Interval; EU=European Union; LB=Lower Bound; O/E=Observed versus Expected; PE=Point Estimate; RP=Reporting Percentage; US=United States.
a: Counts included cases with events of interest that occurred within the risk window-and cases where time-to-onset was 0 or not reported.
b: Poisson exact confidence interval (95% CI).

A review of the results for the US and EU broad analysis (applying a 100% reporting percentage and point estimate incident rate) and the sensitivity analysis (applying a 50% reporting percentage and lower bound incident rate) showed an O/E ratio of <1 in the US and EU for both age groups. A restricted O/E analysis was not required.

MAHs Conclusion Based on the review of the available data, no new safety information was identified during the reporting period for of Bell's palsy. Bell's palsy remains an AESI for Ad26.COV2.S. The MAH will continue to closely monitor these events in this next scheduled PBRER.

Rapporteur assessment comment: No new safety concern is detected here.

Convulsions/Seizures

Although the PBRER reporting period is from 25 February 2021 to 24 August 2021, the O/E analysis covers the period of 25 February 2021 to 31 August 2021.

Results/Discussion

During this reporting period, 233 (125 medically confirmed and 108 medically unconfirmed) cases reporting convulsions/seizures were identified; 228 serious and 5 nonserious reporting a total of 242 events (234 serious, 8 nonserious). Of these 233 cases, 2 was reported from placebo-controlled studies, 5 from open-label studies, and 226 from post-marketing sources. See Table 114 below.

Table 114: Frequency of MedDRA PTs of Interest Involving the Use of Ad26.COV2.S and Reporting Convulsions/Seizures (Events=242)

MedDRA PTs	Number of Events	
	Serious	Nonserious
Seizure	189	1
Generalised tonic-clonic seizure	14	0
Epilepsy	8	0
Tonic clonic movements	7	0
Febrile convulsion	2	4
Seizure like phenomena	3	0
Status epilepticus	3	0
Dreamy state	0	2
Partial seizures	2	0
Postictal state	1	1
Tonic convulsion	2	0
Focal dyscognitive seizures	1	0
Postictal paralysis	1	0
Seizure cluster	1	0
Total	**234**	**8**

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term.

Placebo-controlled Studies

During this reporting period, 2 cases reporting convulsions/seizures were retrieved from placebo-controlled studies. These 2 cases were reported from VAC31518COV3009 (n=1) and VAC31518COV3001 (n=1); reported from the 4.1(b) and the 4.1(b) One case concerned a female aged 64-years-old, and 1 male aged 59-years-old. The TTO was 65 and 188 days. The outcome for the EOI was reported as resolved (n=2). EOI causality was reported as: Company/reporter assessed as not related for both cases.

Open-label Studies [VAC31518COV3012 (Sisonke); and VAC31518COV4007 (Brazil Early Access)]

During this reporting period, 5 cases reporting convulsions/seizures were retrieved from open-label studies; reporting 5 EOIs (4serious, 1 nonserious). Four were reported from VAC31518COV3012 (Sisonke), and 1 from VAC31518COV4007-Brazil Early Access, and 4 concerned females, and 1 male with an age range of 23 to 68 years. The mean and median TTO was 23.2 days and 15days, respectively. The outcome was reported as recovered (n=3), fatal (n=1) and recovering (n=1). The fatal EOI reported was seizure. No concurrent medical conditions were reported; however, it was reported that the patient had "recently undergone dialysis for acute kidney injury with encephalopathy and uraemic gastritis". Dates of the procedure were not reported. It is unknown if an autopsy was performed. The reporter assessed the case as possibly related. EOI causality was reported as: Company/reporter assessed as not related (n=2); Company/reporter assessed as related (n=1); Company assessed as not related with reporter causality not reported (n=1); and Company assessed as not related with reporter causality as possibly related (n=1).

Post-marketing Sources (Including Spontaneous and Solicited Cases)

During this reporting period, 226 cases reporting convulsions/seizures were retrieved from post-marketing sources. These 226 cases reported a total of 235EOI (228 serious, 7 nonserious); most frequently from the US (n=115). Of these 226 cases, 118 concerned males, 89 females, and 19 did not report sex. The age range was 18 to 94 years. The EOI (n≥6) included seizure (n=183), generalized tonic-clonic seizure (n=14), epilepsy (n=8), tonic-clonic movements (n=7), and febrile convulsion (n=6). The mean and median TTO was 4.6 days and 0 days, respectively. Where reported (n=146), the outcome was reported as resolved (n=88), not resolved (n=34), resolving (n=16), fatal (n=5), and resolved with sequelae (n=3). The events with a fatal outcome were seizure (n=3), generalised tonic-clonic seizure (n=1), and status epilepticus (n=1). Company/reporter causality assessed as possibly related for the 3 fatal cases reporting 5 fatal events. Further details regarding these 3 cases are presented in Table 115below.

Table 115: Summary of Cases With Fatal Outcome Reporting Convulsions/Seizures With Use of Ad26.COV2.S (Cases=3; Events=5)

AER# Age (Years)/Sex Medically Confirmed (Yes/No) Country	MedDRA PT of Interest	Time to Onset[a]	Relevant Medical History/Concurrent Conditions
20210500861 59/Female Yes US	Seizure	16 days	Pre-diabetes
20210502010 47/Male Yes US	Generalised tonic-clonic seizure Seizure Status epilepticus	6 days	Leukoencephalopathy, multiple sclerosis, seizures, pulmonary embolism
20210810013 20/Female Philippines	Seizure	Same day	Not reported

There were 4 literature cases reported; three of the 4 cases were from the same article and concerned females aged 18-, 35- and 52-year-old. The EOIs in these 3 cases were seizure (n=2) and epilepsy (n=1). In addition to seizure/epilepsy, cerebral haemorrhage, and thrombocytopenia were also reported in all 3 cases. In 2 cases, superior sagittal sinus thrombosis was coreported, and in 1 case cerebral venous sinus thrombosis was coreported. A medical history of thrombocytopenia was reported for 1 of the patients. The remaining case was from a literature article that concerned multiple patients. Past medical history, concurrent conditions, and concomitant medications were not reported. On unspecified dates, the patients experienced seizure-like phenomena, syncope, chest pain, hypotension, dizziness, vomiting, pallor, hyperhidrosis, tachycardia, anxiety, and nausea. Outcomes for the events were not reported. These events were considered unassessable. The events had a compatible/suggestive temporal relationship, were unlabeled, and had unknown scientific plausibility. There was no information on any other factors potentially associated with the events. This EOI will continue to be monitored via routine PV activities. Review of the cases, including demographics, concomitant medications, concurrent conditions/medical history, outcome, and seriousness received during this reporting period did not identify evidence suggestive of convulsions/seizures being causally associated with Ad26.COV2.S.

O/E Analysis

Results of the broad O/E and sensitivity analysis are presented in Table 116.

Table 116: Broad O/E Analysis Results (Convulsions/Seizures)

	O/E Analysis				Sensitivity Analysis	
Region	Age Range (Years)	Observed Count[a]	O/E ratio (95% CI)[b] (PE, 100% RP)		O/E ratio (95% CI)[b] (LB, 50% RP)	
US	18 to 59	75.08	0.365	(0.287-0.457)	0.729	(0.574-0.914)
	≥60	26.62	0.156	(0.103-0.228)	0.313	(0.205-0.456)
EU	18 to 59	69.46	0.419	(0.326-0.530)	0.954	(0.743-1.206)
	≥60	5.48	0.043	(0.015-0.096)	0.093	(0.032-0.210)

Key: CI=Confidence Interval; EU=European Union; LB=Lower Bound; O/E=Observed versus Expected; PE=Point Estimate; RP=Reporting Percentage; US=United States.
a: Counts included cases with events of interest that occurred within the risk window and cases where time-to-onset was 0 or not reported.
b: Poisson exact confidence interval (95% CI).

A review of the results for the US and EU broad analysis (applying a 100% reporting percentage and point estimate incident rate) and the sensitivity analysis (applying a 50% reporting percentage and lower bound incident rate) showed an O/E ratio of <1 in the US and EU for both age groups. A restricted O/E analysis was not required.

MAHs Conclusion Based on the review of the literature, ongoing/completed clinical studies, relevant cases retrieved from the Company global safety database, and O/E analysis results for the current reporting period, no new safety information was identified during the reporting period for convulsions/seizures.

Rapporteur assessment comment: No new safety concern is detected here.

Encephalitis (Including Acute Disseminated Encephalomyelitis and Meningoencephalitis)

Although the PBRER reporting period is from 25 February 2021 to 24 August 2021, the O/E analysis covers the period of 25 February 2021 to 31 August 2021.

PRAC Rapporteur comments: encephalitis (including ADEM) has been assessed in depth in MSSRs, including cumulative reviews covering a longer time frame than within the current PSUR. Therefore, the data within the PSUR are only briefly described below; and reference is made to the MSSRs (MEA14.5-7).

Results/Discussion

During this reporting period, 159 (74medically confirmed and 85medically unconfirmed) cases reporting encephalitis (including ADEM and meningoencephalitis) were reported. Of these 159 cases, 118 were serious and 41 were nonserious reporting a total of 165 events (114 serious, 51 nonserious). Of these 159 cases, 4 were reported from placebo-controlled studies, 4from open-label studies, and 151 from post-marketing sources (including spontaneous and solicited cases).

MAHs Conclusion Based on the available), safety data it is considered insufficient to establish a causal link between Ad26.COV2.S and inflammatory CNS conditions including encephalitis, ADEM, and meningoencephalitis. The majority of the cases contained insufficient information to support the event and its causal link to the vaccine. CNS inflammatory conditions (including encephalitis, meningoencephalitis and ADEM) remain AESIs for Ad26.COV2.S. The MAH will continue to closely monitor these events.

Rapporteur assessment comment: After the reporting period of this PSUR, encephalitis including ADEM has been further evaluated in depth in the following MSSRs EMEA/H/C/005737/MEA/014.6 and EMEA/H/C/005737/MEA/014.7. It is at present concluded that there is insufficient evidence to support an update of the PI. Further monitoring is important.

Multiple Sclerosis (Including Optic Neuritis)

Although the PBRER reporting period is from 25 February 2021 to 24 August 2021, the O/E analysis covers the period of 25 February 2021 to 31 August 2021.

Results/Discussion

During this reporting period, 26 (18 medically confirmed and 8 medically unconfirmed) cases reporting multiple sclerosis (including optic neuritis) were identified. All of the 26 cases were serious and reported a total of 27 serious events.

Placebo-controlled Studies

During this reporting period, 1 case reporting multiple sclerosis (including optic neuritis) was retrieved from a placebo-controlled study (VAC31518COV3001) and concerned a 38-year-old female from Brazil who experienced a serious optic neuritis. The TTO was 68 days, and the outcome was reported as resolved with sequelae. Company/Reporter causality was assessed as not related.

Open-label Studies [VAC31518COV3012 (Sisonke); and VAC31518COV4007 (Brazil Early Access)]

During this reporting period, 1 case reporting multiple sclerosis (including optic neuritis) was retrieved from an open-label study; 4.1(b) from VAC31518COV3012. This case concerned a 36-year-old female from South Africa who experienced a serious EOI of optic neuritis. The TTO was 19 days, and the outcome was reported as resolving. Bilateral Bell's palsy/optic neuritis is very rare and requires extensive differential diagnosis to confirm diagnosis/rule out other aetiologies. The reported event was assessed to have an indeterminate causal association to vaccination with the available information.

Company causality was considered as not related at this time. Additional information including clinical examinations and diagnosis has been requested for further assessment.

Post-marketing Sources (Including Spontaneous and Solicited Cases)

During this reporting period, 24cases reporting multiple sclerosis (including optic neuritis) were retrieved from post-marketing sources. These 24cases reported25 serious EOIs. Of these 24cases, the most frequently reported country of origin was the US (n=23). Of these 24cases, 17 concerned females and 7 males with reported age range of18 to 71 years.

The most frequently reported EOIs included multiple sclerosis (n=15), optic neuritis (n=7), multiple sclerosis relapse (n=2), and tumefactive multiple sclerosis (n=1). The mean and median TTO were 16.4days and 12 days, respectively. Where reported (n=23), the outcome was reported as not resolved (n=22) and resolving (n=1).

Multiple sclerosis: In total, 17 cases reported a total of 18 EOI of multiple sclerosis including, multiple sclerosis (n=15), multiple sclerosis relapse (n=2), and tumefactive multiple sclerosis (n=1). Most cases were reported in females (13, age range: 18 to 71 years) compared to males (4, age range: 49 to 55years). Of the 17 cases, 8 reported patients with a medical history or concurrent condition of multiple sclerosis. In 5 cases, relevant medical history or concomitant medication was not reported. In the remaining 4 cases, a differential diagnosis of transverse myelitis (n=2), ADEM (n=1), myelitis (n=1) were reported. The TTO range was from 0 to 70 days. Where reported (n=16), the outcome was reported as not resolved (n=15) and resolving (n=1). All cases of multiple sclerosis were reported in the US from the following sources: VAERS database (n=16), and other (n=1).

Optic neuritis: In total, 9 cases reported a total of 9 EOI of optic neuritis. The majority of cases were reported in females (6, age range: 33 to 51 years) compared to males (3, age range: 25 to 53 years). Of the 9 cases reported, 1 reported a patient with concurrent suspected Lyme disease. The TTO range was from 0 to 68 days. The outcome was reported as not resolved (n=7), and resolved with sequelae (n=1), and resolving (n=1). Cases of optic neuritis were received from the following sources: VAERS database (n=7), Eudravigilance (n=1), and VAC31518COV4007-Brazil Early Access (n=1).

Individual case safety report (ICSR) literature cases received during the reporting period were reviewed. There were no literature ICSRs identified. Review of the cases, including demographics, concomitant medications, concurrent conditions/medical history, outcome, and seriousness received during this reporting period is not suggestive of that multiple sclerosis (including optic neuritis) is associated with Ad.26.COV2.S.

O/E Analysis

Results of the broad O/E and sensitivity analysis are presented in Table 123.

Table 123: Broad O/E Analysis Results [Multiple Sclerosis (Including Optic Neuritis)]

O/E Analysis Results					Sensitivity Analysis	
Region	Age Range (Years)	Observed Count[a]	O/E ratio (95% CI)[b] (PE, 100% RP)		O/E ratio (95% CI)[b] (LB, 50% RP)	
US	18 to 59	20.64	0.113	(0.069-0.173)	0.225	(0.139-0.346)
	≥60	2.34	0.035	(0.005-0.115)	0.069	(0.011-0.230)
EU	18 to 59	1.00	0.005	(0.000-0.029)	0.038	(0.001-0.212)
	≥60	0.00	0.000	(0.000-0.057)	0.000	(0.000-0.415)

Key: CI=Confidence Interval; EU=European Union; LB=Lower Bound; O/E=Observed versus Expected; PE=Point Estimate; RP=Reporting Percentage; US=United States.

a: Counts included cases with events of interest that occurred within the risk window, and cases where time-to-onset was 0 or not reported.

b: Poisson exact confidence interval (95% CI).

A review of the results for the US and EU broad analysis (applying a 100% reporting percentage and point estimate incident rate) and the sensitivity analysis (applying a 50% reporting percentage and lower

bound incident rate) showed an O/E ratio of <1 in the US and EU for both age groups. A restricted O/E analysis was not required.

MAHs Conclusion Based on the review of the literature (ie, Section 11), ongoing/completed clinical studies (ie, Sections 7, 8, and 9), relevant cases retrieved from the Company global safety database, and an O/E analysis for the current reporting period and O/E analysis, no new safety information was identified during the reporting period for multiple sclerosis (including optic neuritis).

Rapporteur assessment comment: No new safety concern is detected here.

Narcolepsy

Although the PBRER reporting period is from 25 February 2021 to 24 August 2021, the O/E analysis covers the period of 25 February 2021 to 31 August 2021.

Results/Discussion

During this reporting period, 247 (25 medically confirmed and 222 medically unconfirmed) cases stating to have been reporting narcolepsy were identified. Of these 247 cases, 60 were serious and 187 were nonserious reporting a total of 248 events (27 serious, 221 nonserious). See Table 124 below.

Table 124: Characteristics of Cases Involving the Use of Ad26.COV2.S and Reporting Narcolepsy (Cases=247; Events=248)

Case Characteristics		Number of Cases=247
Sex	Female	133
	Male	82
	NR	32
Age (Years)	18 to 35	38
Minimum: 18	36 to 50	40
Maximum: 92	51 to 64	60
Mean: 52.2	≥65	45
Median: 53	Adult	2
	NR	62

The frequency distribution of the 248 MedDRA PTs of interest reported in these 247 cases is presented in Table 125 below. A single case may contain more than 1 EOI.

Table 125: Frequency of MedDRA PTs of Interest Involving the Use of Ad26.COV2.S and Reporting Narcolepsy (Events=248)

MedDRA PTs	Number of Events	
	Serious	Nonserious
Hypersomnia	9	141
Sleep disorder	15	80
Narcolepsy	3	0
Total	**27**	**221**

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term.

Placebo-controlled Studies

There were no cases retrieved from the search of the Company global safety database.

Open-label Studies [VAC31518COV3012 (Sisonke); and VAC31518COV4007 (Brazil Early Access)]

During this reporting period, 1 case reporting 1 nonserious EOI of hypersomnia. This case was reported from Brazil and concerned a 22-year-old male. The TTO was 0 days, and the EOI outcome was reported as resolved. The Company and reporter causality were assessed as related.

Post-marketing Sources (Including Spontaneous and Solicited Cases)

During this reporting period, 246 cases were retrieved from post-marketing sources reporting 247 EOIs (27 serious, 220 nonserious), and most frequently reported from the US (n=199). Of these 246 cases, 133 concerned females, 81 males, and 32 did not report sex. The age range was 18 to 92 years. The

EOIs reported in these cases included hypersomnia (n=149), sleep disorder (n=95), and narcolepsy (n=3). The mean and median TTO were 3.9 days and 1 day, respectively. Where reported (n=136), the outcome was reported as not resolved (n=68), resolved (n=55), resolving (n=12), and fatal (n=1).

Of the total 247 cases, 2 medically unconfirmed cases with fatal outcome were retrieved from the search. One case concerned a 79-year-old female with unknown medical history and multiple concomitant medications including antihypertensives, anticoagulants, and hypolipidemic medications suggested multiple underlying conditions, who experienced sleep disorders and somnolence in the context of multiple co-reported events such as neurological symptoms, autoimmune disorders, non-infective encephalitis, and other symptoms. Twenty-two days after receiving Ad26.COV2.S, the patient died of multiple organ failure. It was unknown if autopsy was performed. In this case, sleep disorder was related to the patient's multiple comorbidities and coreported events, which was not suggestive of narcolepsy. The second case concerned a 66-year-old male who experienced hypersomnia after vaccination. The patient was a of tobacco user, and had concomitant hypertension, cough, and COPD with concomitant medications including an antihypertensive and hypolipidemic medication. The patient also had a history of COVID-19 infection. An unspecified duration after receiving Ad26.COV2.S., the patient died of pulmonary embolism for which the patient's underlying conditions are risk factors. It was unknown if autopsy was performed. There is no evidence of narcolepsy in this case.

The 3 cases reporting narcolepsy are detailed as follows:

- The first case was from the 4.1(b) with reported MedDRA PTs of Narcolepsy and Pain. It was a medically unconfirmed case of a female of an unspecified age, with an unknown medical history and concurrent conditions. On the same day after receiving Ad26.COV2.S, the patient experienced body ache and could not stay awake. Two days post-vaccination, the body ache resolved while the patient had not recovered from narcolepsy. Limited information is provided on clinical examination, additional symptoms of narcolepsy, and other testing to confirm narcolepsy.
- The second case was from 4.1(b) with reported events including narcolepsy, muscle spasms, gastroenteritis viral, injection site irritation, injection site warmth, urine output increased, injection site pain, injection site erythema, and pyrexia. It was a medically confirmed case of a 73-year-old male, with a medical history of anaphylactic shock and concurrent conditions of multiple allergies, who experienced fever and some redness, irritation, warmth and soreness at the injection site, about an hour after receiving Ad26.COV2.S. Three days post-vaccination the patient experienced intestinal flu symptoms, muscle cramps, and polyuria. The muscle cramp radiated to the lower extremities. The patient also experienced sudden periodic episodes of narcolepsy which lasted 90 minutes or 3 hours. The patient had recovered at the time of reporting. Although muscle spasms were reported, it's unclear if this could be considered as cataplexy. Limited information was provided on clinical examination, additional symptoms of narcolepsy and other testing to confirm narcolepsy.
- The third case was from 4.1(b) with reported PTs including narcolepsy and fatigue. This medically confirmed case described a 46-year-old male with no medical history or concurrent conditions who experienced fatigue and narcolepsy, 1 day after receiving Ad26.COV2.S. The patient was not able to stay awake a few hours after waking up. The event outcome was unknown at the time of the reporting. Limited information was provided on clinical examination, additional symptoms of narcolepsy and other testing to confirm narcolepsy.

There were no literature ICSR identified. All cases were assessed versus the risk window and the BC case definition (Poli F, 2013) and none of the cases reported during the interval met the case definition. Review of the cases, including demographics, concomitant medications, concurrent conditions/medical history, outcome, and seriousness received during this reporting period did not identify any confirmed case of narcolepsy.

O/E Analysis

Results of the broad O/E and sensitivity analysis are presented in Table 126.

Table 126: Broad O/E Analysis Results (Narcolepsy)

	O/E Analysis				Sensitivity Analysis	
Region	**Age Range (Years)**	**Observed count[a]**	**O/E ratio (95% CI)[b] (PE, 100% RP)**		**O/E ratio (95% CI)[b] (LB, 50% RP)**	
US	18 to 59	122.02	0.132	(0.110-0.158)	0.302	(0.251-0.361)
	≥60	79.31	0.221	(0.175-0.275)	0.442	(0.350-0.550)
EU	18 to 59	39.39	**1.398**	**(0.996-1.908)**	**5.359**	**(3.818-7.315)**
	≥60	3.54	**1.493**	**(0.364-4.035)**	**12.604**	**(3.076-34.073)**

Table 126: Broad O/E Analysis Results (Narcolepsy)

	O/E Analysis			Sensitivity Analysis
Region	**Age Range (Years)**	**Observed count[a]**	**O/E ratio (95% CI)[b] (PE, 100% RP)**	**O/E ratio (95% CI)[b] (LB, 50% RP)**

Key: CI=Confidence Interval; EU=European Union; LB=Lower Bound; O/E=Observed versus Expected; PE=Point Estimate; RP=Reporting Percentage; US=United States.

a: Counts included cases with events of interest that occurred within the risk window, and cases where time-to-onset was 0 or not reported.

b: Poisson exact confidence interval (95% CI).

A review of the results for the US and EU broad analysis (applying a 100% reporting percentage and point estimate incident rate) and the sensitivity analysis (applying a 50% reporting percentage and lower bound incident rate) showed an O/E ratio of >1 in the EU only, for both age groups. A restricted O/E analysis was performed for both EU age groups (limited to cases with EOI that occurred within the risk window only). Results of the restricted analysis are presented in Table 127.

Table 127: Restricted O/E Analysis Results (Narcolepsy)

	O/E Analysis				Sensitivity Analysis	
Region	**Age Range (Years)**	**Observed count[a]**	**O/E ratio (95% CI)[b] (PE, 100% RP)**		**O/E ratio (95% CI)[b] (LB, 50% RP)**	
EU	18 to 59	15.73	0.558	(0.317-0.910)	**2.140**	**(1.217-3.489)**
	≥60	0.24	0.101	(0.000-1.761)	0.854	(0.000-14.870)

Key: CI=Confidence Interval; EU=European Union; LB=Lower Bound; O/E=Observed versus Expected; PE=Point Estimate; RP=Reporting Percentage; US=United States.

a: Counts included cases with events of interest with known time-to-onset that occurred within the risk window only.

b: Poisson exact confidence interval (95% CI).

A review of the results for the restricted analysis (applying a 100% reporting percentage and point estimate incident rate) showed an O/E ratio of <1 in the EU for both age groups. A sensitivity analysis (applying a 50% reporting percentage and lower bound incident rate) showed an O/E ratio of >1 in the EU for the 18 to 59 age group.

MAHs Conclusion Although the O/E analysis was higher than 1 in the 18 to 59 age group in EU, the majority (99%) of the EOI reported were hypersomnia and sleep disorder which are not indicative of narcolepsy. Therefore it can be concluded that there is no evidence that narcolepsy is associated with the use of Ad.26.COV2.S.

Rapporteur assessment comment: During the reporting interval, 247 cases of referred to as narcolepsy were reported, however, none of them met the case definition of narcolepsy. The item narcolepsy has been followed in the MSSRs during the reporting interval, for example in EMEA/H/C/005737/MEA/014.2 where it also was concluded that none of the cases met the definition of narcolepsy. No new safety concern is detected here.

Sensorineural Hearing Loss

Although the PBRER reporting period is from 25 February 2021 to 24 August 2021, the O/E analysis covers the period of 25 February 2021 to 31 August 2021.

Results/Discussion

During this reporting period, 345(45medically confirmed and 300 medically unconfirmed) cases reporting SNHL were identified. Of these 345cases, 105were serious and 240 were nonserious reporting a total of 382 events (81 serious, 301 nonserious). None of the cases were reported from open-label studies. See Table 129 below. A single case may contain more than 1 EOI.

Table 129: Frequency of MedDRA PTs of Interest Involving the Use of Ad26.COV2.S and Reporting Sensorineural Hearing Loss (Events=382)

MedDRA PTs	Number of Events	
	Serious	Nonserious
Tinnitus	28	273
Hypoacusis	8	26
Deafness	28	0
Deafness unilateral	8	0
Auditory disorder	2	2
Deafness neurosensory	3	0
Deafness transitory	2	0
Audiogram abnormal	1	0
Ototoxicity	1	0
Total	**81**	**301**

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term.

Placebo-controlled Studies

During this reporting period, 1 case reporting SNHL was retrieved ((VAC31518COV3001). This case concerned a male with unspecified age from the US who experienced a nonserious EOI of tinnitus. The TTO was 29 days, and the outcome was reported as resolving. Company causality was assessed as not related with the reporter causality assessed as related.

Open-label Studies [VAC31518COV3012 (Sisonke); and VAC31518COV4007 (Brazil Early Access)]

There were no cases retrieved from the search of the Company global safety database.

Post-marketing Sources (Including Spontaneous and Solicited Cases)

During this reporting period, 344cases reporting SNHL were retrieved from post-marketing sources; reporting 381 EOIs (81 serious, 300 nonserious), and the most frequently reported was from the US (n=198). 206 concerned females, 109 males, and 29 did not report sex. The age range was 17 to 100 years. The most frequently reported EOIs (n≥4) included tinnitus (n=300), hypoacusis (n=34), deafness (n=28), deafness unilateral (n=8), and auditory disorder (4). The mean and median TTO was 7.7 days and 1 day, respectively. Where reported (n=313), the outcome was not resolved (n=205), resolving (n=53), resolved (n=52), and resolved with sequelae (n=3). There were no literature ICSR identified.

The majority of the 345 cases reported isolated tinnitus (n=267). During the reporting period of this PBRER, a signal was identified for this event, based on disproportionate reporting. A cumulative review through 19 May 2021 concluded that tinnitus was to be considered as a post-vaccine ADR and the event was added as an ADR to the CCDS. Results of case evaluations for tinnitus up to the DLD of the current PBRER remain consistent with the conclusions of the cumulative signal evaluation.

In 78 of the 345 cases, the reported events referred to bi-or unilateral deafness and/or hypoacusis, auditory disorders or otoxicity (with or without tinnitus). Latency of the event ranged from 0 to 118 days (median =3 days). Most of the cases documented an alternate aetiology for the event and/or lacked a diagnostic work-up for the hearing loss. Four cases specifically reported that the patient experienced SNHL. Two of these cases lacked diagnostic information and in 2 cases diagnostic test results consistent with SNHL were reported.

- A 53-year-old female with acute hearing loss the same day of vaccination and results of tests conducted 6 days later included: Rinne tuning fork negative on right side, positive on left side; normal tympanometry, and Weber tuning fork test result central. The event was resolving at time of reporting (no information on treatment regimen provided).
- A 57-year-old female with underlying risk factor of autoimmune disease/Sjogren syndrome who 3 days after receiving the vaccine experienced deafness in the right ear and severe headache. The patient was examined at the ER and test results included Weber lateralizing to the left, Rinne negative on the left, and stable Romberg. Two days later, the patient experienced weakening and discernment in both ears. Cerumen in the left ear was removed, and drums were found to be somewhat white and non-transparent. Audiogram indicated virtual deafness in the right ear, and hearing in the physiological range in the left ear. The patient was treated with glucocorticoids (decortin)/acetylcysteine and subsequently with methylprednisolone; the patient had not recovered from the hearing loss at the time of reporting.

O/E Analysis

An analysis was performed separately for SNHL without tinnitus and for tinnitus alone (see Appendix 6.1 for full methodology to include: exposure calculations, risk windows, background incident rates, and search strategy. Results of the broad O/E and sensitivity analysis are presented in Table 130.

Table 130: Broad O/E Analysis Results [1. Sensorineural Hearing Loss Without Tinnitus, 2. Tinnitus]

		O/E Analysis				Sensitivity Analysis	
AESI/PT	**Region (Risk window, days)**	**Age Range (Years)**		**Observed Count[a]**	**O/E ratio (95% CI)[b] (PE, 100% RP)**	**O/E ratio (95% CI)[b] (LB, 50% RP)**	
Sensorineural Hearing Loss *w/o tinnitus*	US (1-21)	18 to 59	27.08	0.154	(0.102-0.224)	0.758	(0.500-1.102)
		≥60	15.79	0.106	(0.060-0.173)	0.212	(0.121-0.346)
	EU (1-21)	18 to 59	22.93	0.136	(0.086-0.204)	0.667	(0.423-1.002)
		≥60	7.06	0.057	(0.023-0.117)	0.114	(0.046-0.235)
- Tinnitus	US (1-21)	18 to 59	108.08	0.047	(0.039-0.057)	0.250	(0.205-0.302)
		≥60	53.45	0.037	(0.028-0.048)	0.262	(0.197-0.343)
	EU (1-21)	18 to 59	109.98	0.050	(0.041-0.060)	0.265	(0.218-0.319)
		≥60	9.90	0.008	(0.004-0.015)	0.058	(0.028-0.108)
Sensorineural Hearing Loss *w/o tinnitus*	US (1-14)	18 to 59	24.08	0.204	(0.131-0.303)	**1.002**	**(0.642-1.489)**
		≥60	12.79	0.128	(0.068-0.221)	0.257	(0.136-0.441)
	EU (1-14)	18 to 59	21.93	0.190	(0.119-0.288)	0.935	(0.585-1.416)
		≥60	7.06	0.084	(0.034-0.172)	0.168	(0.068-0.345)
- Tinnitus	US (1-14)	18 to 59	105.08	0.068	(0.056-0.083)	0.361	(0.296-0.438)
		≥60	51.45	0.053	(0.039-0.069)	0.377	(0.281-0.495)
	EU (1-14)	18 to 59	109.98	0.073	(0.060-0.088)	0.388	(0.319-0.467)
		≥60	8.90	0.011	(0.005-0.021)	0.077	(0.035-0.147)

Key: CI=Confidence Interval; EU-European Union; LB=Lower Bound; O/E=Observed versus Expected; PE=Point Estimate; RP=Reporting Percentage; US=United States; W/O=Without

a: Counts included cases with events of interest that occurred within the risk window, and cases where time-to-onset was 0 or not reported.

b: Poisson exact confidence interval (95% CI).

*: Tinnitus is not an AESI but falls under the subcategory of AESI: Sensorineural Hearing Loss.

A review of the results for the US and EU broad analysis (applying a 100% reporting percentage and point estimate incident rate) for both sensorineural hearing loss without tinnitus and tinnitus alone showed an O/E ratio of <1 in both the US and EU for both risk windows (1 to 21, 1 to 14days) and age groups. A sensitivity analysis (applying a 50% reporting percentage and lower bound incident rate) showed an O/E ratio of >1 for sensorineural hearing loss without tinnitus in the US (risk window: 1 to 14 days) 18-to-59-year age group only. A restricted O/E analysis was performed for the US (risk window: 1 to 14 days) 18-to-59-year age group (limited to cases with EOI that occurred within the risk window only) for this AESI. Results of the restricted analysis are presented in Table 131.

Table 131: Restricted O/E Analysis Results [1. Sensorineural Hearing Loss Without Tinnitus]

O/E Analysis							Sensitivity Analysis	
AESI/PT	Region	Risk window (days)	Age Range (Years)	Observed count[a]	O/E ratio (95% CI)[b] (PE, 100% RP)		O/E ratio (95% CI) (LB, 50% RP)	
Sensorineural Hearing Loss w/o tinnitus	US	1-14	18 to 59	12.22	0.103	(0.054-0.180)	0.508	(0.264-0.884)

Key: CI=Confidence Interval; LB=Lower Bound; O/E=Observed versus Expected; PE=Point Estimate; RP=Reporting Percentage; US=United States; w/o=Without.

a: Counts included cases with events of interest with known time-to-onset that occurred within the risk window only.

b: Poisson exact confidence interval (95%CI)..

MAHs conclusion Tinnitus is considered associated with the use of Ad26.COV2.S and has been added as an ADR in the CCDS during the reporting period of this PBRER. None of the cases met the case definition of SNHL. Considering the plausible time to onset in the remaining 2 cases and diagnostic workup results, the causality of the vaccine with SNHL could not be excluded in these cases.

An O/E analysis on cases reporting SNHL without tinnitus showed O/E ratios <1 in the restricted analysis, irrespective of region, age group and risk window applied (21 and 14days). Altogether, at present, there is insufficient evidence to establish a causal association between Ad26.COV2.S and SNHL. Events of SNHL will continue to be closely monitored.

Rapporteur assessment comment:

As an outcome of the assessment of the June 2021 MSSR, it was concluded that tinnitus should be added as an ADR with frequency rare in the SmPC, which has thereafter been implemented. No new safety concern is detected here.

Transverse Myelitis

A cumulative review was requested by EMA in the Final Assessment Report EMEA/H/C/005737/MEA/014.4 received on 02 September 2021 for the MSSR dated 01 August 2021 to 31 August 2021. The request was "*a cumulative review should be presented, including a summary of all case narratives, and comments regarding need for updates of the PI/RMP*" .

PRAC rapporteur comments; transverse myelitis has been assessed in depth in MEA 14.5, and in an subsequent variation which is ongoing (II-35). Therefore, only limited details on the data submitted within the PSUR, covering a shorter time frame is included below)

Results/Discussion

During this reporting period, 41 (33 medically confirmed and 8 medically unconfirmed) cases reporting transverse myelitis were identified. All of the 41 cases were serious and reported a total of 51 serious EOI.

Of these 41 cases, 2 were reported from open-label study and 39 from post-marketing sources (including spontaneous and solicited cases). None of the cases were reported from placebo-controlled studies. An overview of the 41 cases is presented in Table 132 below.

See Table 133 below. A single case may contain more than 1 EOI.

Table 133: Frequency of MedDRA PTs of Interest Involving the Use of Ad26.COV2.S and Reporting Transverse Myelitis (Events=51)

MedDRA PTs	Number of Serious Events
Myelitis transverse	29
Demyelination	9
Myelitis	7
Neuromyelitis optica spectrum disorder	4
Autoimmune demyelinating disease	2
Total	**51**

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term.

Placebo-controlled Studies

There were no cases retrieved from the search of the Company global safety database.

Open-label Studies [VAC31518COV3012 (Sisonke); and VAC31518COV4007 (Brazil Early Access)]

During this reporting period, 2 cases were retrieved reporting transverse myelitis from an open-label study (VAC31518COV3012); reporting 2 serious EOIs. Both the cases were from South Africa and concerned 2 males (45-year-old and 56-years-old). The TTO was reported as 67 days and 111 days with a mean of 89 days. Where reported (1), the outcome was reported as resolving. EOI causality was reported as Company/reporter assessed as not related in 1 case; and Company assessed as not related with reporter causality not reported in the other case.

Post-marketing Sources (Including Spontaneous and Solicited Cases)

During this reporting period, 39 cases were retrieved reporting transverse myelitis from post-marketing sources; reporting 49 serious EOIs, and most frequently from the US (n=30). 21 concerned females and 18 males. The age range was 18 to 75years. The EOIs reported in these cases included myelitis transverse (n=27), demyelination (n=9), myelitis (n=7), neuromyelitis optica spectrum disorder (n=4), and autoimmune demyelinating disease (n=2). Where reported (n=43), the mean and median TTO was 18.8 days and 14days, respectively. Where reported (n=44), the outcome was reported as not resolved (n=35), resolving (n=7), and resolved (n=2). There were no literature ICSRs identified.

O/E Analysis

Results of the broad O/E and sensitivity analysis are presented in Table 134.

Table 134: Broad O/E Analysis Results (Transverse Myelitis)

	O/E Analysis				Sensitivity Analysis	
Region	**Age Range (Years)**	**Observed Count[a]**	**O/E ratio (95% CI)[b] (PE, 100% RP)**		**O/E ratio (95% CI)[b] (LB, 50% RP)**	
US	18 to 59	25.00	**2.157**	**(1.396-3.184)**	**4.314**	**(2.792-6.369)**
	≥60	4.00	0.956	(0.260-2.447)	**1.912**	**(0.521-4.895)**
EU	18 to 59	4.93	**1.128**	**(0.363-2.648)**	**7.898**	**(2.538-18.534)**
	≥60	1.06	**4.062**	**(0.123-21.749)**	**21.665**	**(0.656-115.996)**

Key: CI=Confidence Interval; EU=European Union; LB=Lower Bound; O/E=Observed versus Expected; PE=Point Estimate; RP=Reporting Percentage; US=United States.

a: Counts included cases with events of interest that occurred within the risk window, and cases where time-to-onset was 0 or not reported.

b: Poisson exact confidence interval (95% CI).

. Results of the restricted analysis are presented in Table 135.

Table 135: Restricted O/E Analysis Results (Transverse Myelitis)

O/E analysis					Sensitivity Analysis	
Region	Age Range (Years)	Observed Count[a]	O/E ratio (95% CI)[b] (PE, 100% RP)		O/E ratio (95% CI)[b] (LB, 50% RP)	
US	18 to 59	22.00	**1.898**	**(1.190-2.874)**	**3.796**	**(2.379-5.748)**
	≥60	3.00	0.717	(0.148-2.095)	**1.434**	**(0.296-4.190)**
EU	18 to 59	3.93	0.899	(0.241-2.321)	**6.296**	**(1.689-16.244)**
	≥60	1.06	**4.062**	**(0.123-21.749)**	**21.665**	**(0.656-115.996)**

Key: CI=Confidence Interval; EU=European Union; LB=Lower Bound; O/E=Observed versus Expected; PE=Point Estimate; RP=Reporting Percentage; US=United States.

a: Counts included cases with events of interest with known time-to-onset that occurred within the risk window only.

b: Poisson exact confidence interval (95% CI).

MAHs conclusion Based on review of available data no new safety information was identified during the reporting period for transverse myelitis.

Rapporteur assessment comment:

Transverse myelitis has been further evaluated after the cut-off for this procedure and deemed associated with the vaccine (MEA 14.5). An ongoing procedure (after the cut-off for this PSUR) are evaluating the inclusion of transverse myelitis as an ADR in section 4.8 of the SmPC (EMEA/H/C/005737/II/0035).

2.3.4.5. Vascular Disorders

Cerebrovascular Events

Although the PBRER reporting period is from 25 February 2021 to 24 August 2021, the O/E analysis covers the period of 25 February 2021 to 31 August 2021.

Results/Discussion

During this reporting period, 913 (599 medically confirmed and 314 medically unconfirmed) cases reporting cerebrovascular events were identified; 911 serious and 2 nonserious reporting 1,248 events (1,244 serious, 4 nonserious). See Table 136 below.

Table 136: Characteristics of Cases Involving the Use of Ad26.COV2.S and Reporting Cerebrovascular Events (Cases=913; Events=1,248)

Case Characteristics		Number of Cases=913
Sex	Female	515
	Male	382
	NR	16
Age (Years)	<18	1
Minimum: 17	18 to 35	105
Maximum: 103	36 to 50	205
Mean: 56	51 to 64	277
Median: 57	≥65	261
	Adult	3
	Elderly	1
	NR	60
Sources	Clinical study (non-interventional; solicited)	2
	Clinical study (non-interventional; non-solicited)	1

	Clinical study (Interventional; Non-solicited)	65
	Spontaneous	845
Country	US	712
	Germany	33
	South Africa	26
	Italy	22
	France	19
	Netherlands	19
	Spain	15
	Belgium	10
	Brazil	10
	Poland	6
	Colombia	4
	Ireland	4
	Philippines	4
	United Kingdom	4
	Austria	3
	Denmark	3
	Estonia	3
	Korea, Republic of	3
	Portugal	3
	Greece	2
	Slovenia	2
	Argentina	1
	Iceland	1
	Japan	1
	Lesotho	1
	Puerto Rico	1
	Sweden	1
Event Characteristics		**Number of Events=1,248**
Seriousness (Event Level)[a]	Nonserious	4
	Serious	1244
Outcome (Event Level)[a]	Not resolved	524
	Resolved	186
	Resolving	117
	Fatal	111
	Resolved with sequelae	15
	NR	295

Key: NR=Not Reported; US=United States.

a: Seriousness and outcome have been presented for the events of interest. A single case may report more than 1 event of interest.

The frequency distribution of the 1,248 MedDRA PTs of interest reported in these 913 cases involving the use of Ad26.COV2.S and reporting cerebrovascular events is presented in Table 137 below.

Table 137: Frequency of MedDRA PTs of Interest Involving the Use of Ad26.COV2.S and Reporting Cerebrovascular Events (n=1,248)

MedDRA PTs	Number of Events[a]	
	Serious	Nonserious
Cerebrovascular accident	370	0
Hemiparesis	113	0
Transient ischaemic attack	92	1
Cerebral venous sinus thrombosis	80	0
Cerebral haemorrhage	71	0
Ischaemic stroke	67	0
Cerebral thrombosis	52	0
Cerebral infarction	46	0
Hemiplegia	37	0
Haemorrhagic stroke	22	0
Transverse sinus thrombosis	20	0
Subarachnoid haemorrhage	19	0
Cerebral venous thrombosis	18	0
Cerebral artery occlusion	16	0
Superior sagittal sinus thrombosis	13	0
Embolic stroke	13	0
Intracranial aneurysm	10	0
Carotid artery occlusion	10	0
Subdural haematoma	9	0
Cerebral artery thrombosis	9	0
Haemorrhage intracranial	9	0
Cerebral haematoma	8	0
Carotid artery stenosis	8	0
Lacunar infarction	7	0
Hemiparaesthesia	7	0
Carotid artery thrombosis	6	0
Cerebral ischaemia	5	0
Intraventricular haemorrhage	5	0
Ischaemic cerebral infarction	5	0
Thalamic infarction	5	0
Basal ganglia infarction	4	0
Cerebral artery embolism	4	0
Cerebrovascular disorder	4	0
Hemianaesthesia	4	0
Brain stem stroke	3	0
Cerebellar stroke	3	0
Cerebellar infarction	3	0
Lacunar stroke	3	0
Cerebral small vessel ischaemic disease	3	0
Brain stem thrombosis	3	0
Basal ganglia stroke	3	0
Vertebral artery thrombosis	2	0
Vertebral artery stenosis	2	0
Spinal cord infarction	2	0
Cerebellar haemorrhage	2	0
Thrombotic stroke	2	0
Carotid arteriosclerosis	1	1
Ruptured cerebral aneurysm	2	0
Carotid artery dissection	2	0

Subdural haemorrhage	1	1
Haemorrhagic transformation stroke	2	0
Thrombotic cerebral infarction	2	0
Brain stem infarction	2	0
Basilar artery thrombosis	2	0
Cerebral congestion	1	1
Vertebral artery dissection	2	0
Carotid endarterectomy	2	0
Basal ganglia haemorrhage	2	0
Thalamus haemorrhage	1	0
Cerebral revascularisation	1	0
Hypoxic-ischaemic encephalopathy	1	0
Vertebral artery occlusion	1	0
Cerebellar artery occlusion	1	0
Cerebellar embolism	1	0
Basilar artery occlusion	1	0
Cerebral hypoperfusion	1	0
Carotid angioplasty	1	0
Brain hypoxia	1	0
Cerebral artery stenosis	1	0
Post stroke depression	1	0
Hemihyperaesthesia	1	0
Brain stem haemorrhage	1	0
Dural arteriovenous fistula	1	0
Spinal artery thrombosis	1	0
Carotid artery disease	1	0
Spinal cord haematoma	1	0
Cerebral endovascular aneurysm repair	1	0
Cerebrovascular insufficiency	1	0
Carotid revascularisation	1	0
Basilar artery stenosis	1	0
Amaurosis fugax	1	0
Cerebral vasoconstriction	1	0
Total	**1244**	**4**

Key: MedDRA=Medical Dictionary for Regulatory Activities; n=Number of Cases; PT=Preferred Term.

a: A single case may report more than 1 MedDRA PT of interest.

Placebo-controlled Studies

During this reporting period, 49 cases reporting cerebrovascular events were retrieved from placebo-controlled studies; 31 from VAC31518COV3001, 14 from VAC31518COV3009, 1 each from VAC31518COV2009, VAC31518COV1002, VAC31518COV1001, VAC31518COV2001. A total of 58 EOI (56 serious, 2 nonserious) were reported most frequently from the US (n=22). Of the 49 cases, 28 concerned males and 21 females with an age range of 25 to 82 years.

TTO was reported in 43 cases, with a mean and median TTO of 88.6 days and 70 days, respectively; 10 reported a latency within the risk window of 28 days; 6 of these 10 patients had underlying risk factors for cerebrovascular events, such as cerebral ischaemia, hypertension, hyperlipidaemia, obesity, coronary artery stenosis/bypass, or alcohol abuse, and 2 of the 4 patients without reported risk factors were older than 60 years, with age being a risk factor per se.

The remaining 2 cases referred to a 25-year-old male who experienced transverse sinus venous thrombosis and secondary cerebral hemorrhage 18 days after vaccination, and hemiparesis in a 49-year-old female 27 days after vaccination, which resolved. The outcome for the EOI were reported as resolved (n=34), resolved with sequelae (n=10), resolving (n=10), not resolved at the time of reporting (n=3), and fatal (n=1). The 1 case with fatal outcome involved limited information on cerebral haemorrhage 12 days after vaccination in a 65-year-old female with underlying hypertension and hypothyroidism. In 50 events the Company/reporter causality was assessed not related. In 6 events, the Company causality was assessed as not related; however, reporter causality was assessed as possible (n=1) and related (n=5). For 2 EOI (ie, transverse sinus venous thrombosis and secondary cerebral hemorrhage in the 25-year-old male patient described above), the Company causality was assessed as related and reporter causality as not related. In addition to the advanced patient age reported in 23 of 49 cases, at least 1 or several

additional risk factors for cerebrovascular events were reported in all 44 cases: hypertension (n=28), tobacco use (n=14), hypercholesterolaemia/hyperlipidaemia (n=13), overweight/obesity (n=13), diabetes mellitus (n=9), depression (n=8), alcohol (ab)use (n=7) sleep disorder/insomnia/sleep apnoea (n=6), coronary artery disease/bypass (n=5), atrial fibrillation (n=4), previous cerebrovascular accident (n=4), HIV infection (n=3), malignancies (n=2), migraine, myocardial ischaemia, myocardial infarction, cerebral ischaemia, arteriovenous malformation, and tachycardia (n= 1 each).

Open-label Studies (VAC31518COV3012 [Sisonke]; and VAC31518COV4007 [Brazil Early Access])

During this reporting period, 17 cases reporting cerebrovascular events were retrieved from open-label studies; 16 from VAC31518COV3012, 1 from VAC31518COV4007; reporting19 serious EOI, and most frequently from South Africa (n=16). One concerned a male and 16 females with an age range of 18 to 60 years. The EOI included cerebrovascular accident (n=8), 2 each of subarachnoid hemorrhage, transient ischemic attack, cerebral venous sinus thrombosis, and cerebral hemorrhage, and 1 each of hemiparesis, cerebral thrombosis, hemiplegia. A latency from vaccination to event onset was reported in 16 of 17 cases, with a mean and median TTO of 15.5 days and 11 days, respectively. In 12 cases, a latency within the risk window of 28 days was reported. The outcome of the EOI was reported as follows: fatal (n=2), not resolved (n=9), resolved (n=2), and resolving (n=6). EOI causality assessed: Company/reporter not related (n=3) Company/reporter as related (n=2); Company assessed as not related with reporter causality not reported (n=13); and Company assessed as related with reporter causality not reported (n=1). The 1 fatal case reported 2 fatal events of cerebral thrombosis and subarachnoid haemorrhage (latency 11 days) in a 25-year-old female (platelet count was 9,000, reference range or units not provided). Although the patient's use of hormonal contraception and a sedentary lifestyle may have contributed to the event, based on evolving knowledge of TTS, per definition from BC and considering the low platelet count and temporal relationship to vaccination, the events are assessed to have a plausible relationship with the vaccination. Ten (10) of 17 cases reported 1 or several risk factors for cerebrovascular events: oral contraceptive ethinylestradiol/levonorgestrel (n=4), alcohol and/or tobacco use (n=3), hypertension (n=2), a previous cerebrovascular accident (n=2), lack of exercise, aortic valve incompetence/replacement, HIV infection, systemic lupus erythematosus, and diabetes mellitus (n=1 each).

Post-marketing Sources (Including Spontaneous and Solicited Cases)

During this reporting period, 847 cases reporting cerebrovascular events were retrieved from post-marketing sources; and a total of 1,171 EOI (1,169 serious, 2 nonserious) and the most frequently was from the US (n=690). 353 concerned males, 478 females, and 16 did not report sex. The age range was 17 to 103 years.

The EOI (n≥35) included cerebrovascular accident (n=348), hemiparesis (n=109), transient ischaemic attack (n=82), cerebral venous sinus thrombosis (n=78), cerebral haemorrhage (n=67) ischaemic stroke (n=55), cerebral thrombosis (n=50), cerebral infarction (n=45), and hemiplegia (n=35). The mean and median TTO were 17.1 days and 11 days, respectively. In 107 cases, 128 EOI involved venous sinus thromboses: cerebral venous sinus thrombosis (n=78), transverse sinus thrombosis (n=19), cerebral venous thrombosis (n=18), and superior sagittal sinus thrombosis (n=13). Latency from vaccination to event onset was reported for 116 of 128 EOI, with 98 EOI occurring within the risk window of 28 days (ranging from day 0 to day 28). With respect to patient's age, 115 EOI were reported in 96 adult patients, 11 EOI occurred in 9 elderly patients from 65 to 78 years of age, and 2 EOI occurred in 2 patients which did not report age/age group. A total of 57 EOI were reported in 45 patients with underlying risk factors for the development of cerebrovascular events. Eleven EOI of venous sinus thromboses had a fatal outcome, 52 had not resolved, 10 were resolved, 13 were resolving, and 42 EOI did not report an outcome. Regarding event outcome of the 1,171 EOI, reported a fatal outcome (n=108), not resolved (n=512), resolved (n=150), resolved with sequalae (n=5), were resolving

(n=101), and not reported (n=295). Of the 1,171 EOI, 185 were reported outside the risk window of 28 days, with latencies from vaccination until event onset ranging from day 29 to day 142, 841 were reported with a latency within the risk window, ranging from day 0 to day 28, and 145 did not report the latency. Of the 986 EOI occurring within the risk window of 28 days or without reported latency, 263 occurred in 200 elderly patients with an age range from 65 to 103 years, 658 occurred in 467 adults with an age range from 18 to 64 years, 1 occurred in a 17-year-old adolescent, and 64were reported in 56 patients of unspecified age. Of these 724 patients, 347 had underlying risk factors for the development of cerebrovascular events, such as hypertension (n=172), diabetes mellitus (n=91), hyperlipidaemia/blood cholesterol increased or abnormal (n=48), overweight/obesity (n=45), depression (n=33), migraine (n=29), coronary artery disease/bypass/occlusion/stent insertion and/or (congestive) cardiac failure (n=29), tobacco use (n=28), a medical history of cerebrovascular accident (n=25), malignancies (n=25); such as breast cancer, bladder cancer, prostate cancer, malignant brain neoplasm, colon adenocarcinoma), alcohol (ab)use (n=21), atrial fibrillation (n=18), sleep disorders such as insomnia and sleep apnoea syndrome (n=15), oral contraceptives (n=13); ethinylestradiol or levenorgestrel), (deep vein) thrombosis (n=11), myocardial infarction (n=7), cardiomyopathy (n=6), rheumatoid arthritis (n=5), valvular heart disease (n=5), autoimmune thyroiditis (n=4), transient ischaemic attack (n=4), systemic lupus erythematosus (n=4), cardiovascular disorder (n=3), arteriosclerosis (n=2), intracranial aneurysm (n=2), myocardial ischaemia (n=2), pulmonary embolism (n=2), reduced mobility (n=2, bedridden, wheelchair use), coagulopathy, atrial septal defect, and HIV infection (n=1 each). Three-hundred seventy-seven (n=377) cases were reported without risk factors; however, 76 of these pertained to elderly patients older than 65 years of age, with advanced age itself representing a risk factor. Of the remaining 301 cases without reported risk factors and referring to patients below the age of 65, 74 (involving 93 EOI) concerned patients 40 years or younger at the time the EOI occurred. Latencies from vaccination to event onset were reported for 81 of 93 EOI and ranged from day 0 to day 26. Of the 93 EOI, 11 involved a fatal outcome (in 8 cases), 12 resolved, 8 were resolving, 38 had not resolved at the time of reporting, and no outcome was reported for the remaining 24EOI.

The 8 cases with fatal EOI pertained to 2 female and 6 male patients between 23 and 37 years of age. Three of these 8 cases reported cerebral thrombotic events in the context of thrombocytopenia and were thus indicative of TTS. In all 3 cases, a causal relationship between the vaccination and the EOI was considered possible or plausible based on the biochemical and clinical course as well as the evolving knowledge of TTS, per definition from BC; notably, 1 of these cases was confounded by elevated levels of Von Willebrand factor:

- A 37-year-old female experienced headache, malaise, tiredness, fever at 39°C, flu-like symptoms, angina tonsillitis, myalgia and arthralgia within a few days after vaccination with Ad26.COV2.S. Ten days after the vaccination, the patient was diagnosed with acute deep popliteal venous thrombosis of all veins of the right leg, the femoral vein was transient and treatment was with heparin, tinzaparine (10.000 once a day) despite thrombocytopenia at 25g/L. Two days later, the patient experienced disseminated intravascular coagulation and cerebral haemorrhage facilitated by venous thrombosis of sagittal sinus thrombosis, thrombocytopenia due to vaccine-induced prothrombotic immune thrombocytopenia and anticoagulation. Polyvalent immunoglobulins were started, tinzaparine was discontinued and switched to danaparoid. The patient died 13 days after vaccination due to thrombosis, intracerebral haemorrhage, and thrombocytopenia which was confirmed by autopsy. This case was commented by 4 experts and it was concluded that the biochemical and clinical course are strongly in favour of TTS and fit the diagnosis of TTS, hence a causal relationship to the vaccine is probable.

MAH Comments: Anti-platelet antibody test and heparin-induced thrombopenia test were positive. Although the use of heparin may have contributed, based on evolving knowledge of TTS (per definition

from BC), considering the low platelet count prior to heparin use and temporal relationship to vaccination, the events are assessed to have a plausible relationship with vaccination.

- A 34-year-old male experienced sinus vein thrombosis of transverse sinus left, hemorrhage intracerebral, and immune thrombocytopenia, 13 days after vaccination with Ad26.COV2.S. CT angiography results showed sinus venous thrombosis and a head CT scan showed intracerebral hemorrhage and sinus vein thrombosis. The patient died of sinus vein thrombosis of transverse sinus left, ITP, hemorrhage intracerebral, and brain death on an unspecified date.

MAH Comments: The information available precludes a complete and meaningful assessment. The occurrence of thrombosis of venous sinuses could represent background incidence of such events in the general population. However, a relationship with Ad26.COV2.S cannot be ruled out and thus the relationship is considered indeterminate.

- A 36-year-old male with no reported medical history experienced thrombocytopenia, portomesenteric vein thrombosis, cerebral arterial thrombosis, and anti-platelet antibody 6 days after vaccination with Ad26.COV2.S. Urine drug screen was positive for benzodiazepines. Eleven days after vaccination, platelet count was 14,000, fibrin D-dimer was 128,000, COVID-19 PCR test was negative; the patient died from middle cerebral artery infarct, multi-organ failure and stroke. Enzyme-linked Immunoassay (ELISA) test result was positive (no details provided) and Von Willebrand's factor was high (severe reactive elevation); Factor VIII (coagulative) 299.2 (50.0 to 150.0), Von Willebrand factor (antigenic) 488.3 (60.0 to 150.0), Von Willebrand factor (ristocetin cofactor) 374.1 (60.0 to 150.0), and Von Willebrand factor (ratio) 0.77.

MAH Comments: High Von Willebrand's factor confounded the events. Based on the evolving knowledge of TTS, per definition from BC), considering the low platelet count and temporal relationship to vaccination, the event(s) are considered to have a plausible relationship with vaccination. The other 5 cases did not report thrombocytopenia and there was limited information regarding the clinical course of the events, results from lab tests, imaging, or autopsy. The paucity of information provided prevented an informed medical assessment, however, a causal association between the vaccine and the reported events could not be excluded due to a reasonable temporal relationship:

- A 36-year-old healthy male who did not suffer from any previous pathology experienced pain and fever a few days after receiving Ad26.COV2.S. The patient’s sister mentioned that the patient did not remember his name or age (confusion). Ten days after the vaccination, symptoms worsened, a cardiovascular stroke was diagnosed, and the patient was admitted to ICU. One day later the patient died of multiorgan failure. An autopsy was performed, but no results reported. The attending physicians established a link between the vaccine and multiple thrombi.

MAH Comments: This medically unconfirmed case lacks important information from patient’s medical history and concomitant conditions. Also results of autopsy, imaging, and other lab data to confirm the cause of death.

- A 35-year-old female experienced persistent headache after receiving Ad26.COV2.S and died 11 days after the vaccination due to non-traumatic subarachnoid haemorrhage. An autopsy was performed but no results and no further event details were available.

MAH Comments: This event is considered unassessable. The event has a compatible/suggestive temporal relationship, is unlabeled, and has unknown scientific plausibility. There is no information on any other factors potentially associated with the event.

- A 37-year-old healthy male with no pre-existing medical conditions experienced fever, headache, and muscle pain on the day of vaccination with Ad26.COV2.S was treated with paracetamol. Nine days later, the patient had a sudden nosebleed and seizure and was unable to breathe properly.

The patient received cardiopulmonary resuscitation and was diagnosed with cardiac arrest accompanied by arrhythmia in the hospital, and cerebral hemorrhage was found through computed tomography. The patient's blood pressure started to drop excessively and died 2 days later of cardiac arrest and cerebral hemorrhage.

MAH Comments: This event is considered unassessable. The event has a compatible/suggestive temporal relationship, is unlabeled, and has unknown scientific plausibility. There is no information on any other factors potentially associated with the event. □ A 36-year-old male with no medical history or concurrent conditions experienced ictus on an unspecified date after receiving Ad26.COV2.S. Two weeks after vaccination the patient died due to ictus. No concomitant medications were reported. It was unspecified if an autopsy was performed. No other information was provided.

MAH Comments: This case is difficult to assess in the absence of the patient's medical history, concomitant medications, course of events, imaging results, or laboratory data to confirm the diagnosis.

- A 23-year-old male with no past medical history, no concurrent conditions or concomitant medications experienced headache and was feeling unwell around an hour after the vaccination with Ad26.COV2.S. The symptoms got worse in the weekend. The next day, the patient experienced fits and vomiting. The patient was put into an induced coma and experienced brain bleed from and died 4 days after the vaccination. It was unknown if an autopsy was performed.

MAH Comments: This medically unconfirmed case is difficult to assess due to limited information provided on medical history, concomitant medication, and clinical course of the events, and no imaging or laboratory data provided to confirm the diagnosis. However, regarding the compatible time to onset the causality of the vaccine cannot be excluded.

O/E Analysis

Cerebrovascular events-haemorrhagic

Results of the broad O/E and sensitivity analysis for cerebrovascular events (haemorrhagic) are presented in Table 138.

Table 138: Broad O/E Analysis Results (Cerebrovascular Events: Haemorrhagic)

		O/E Analysis				Sensitivity Analysis	
Region	**Sex**	**Age Range (Years)**	**Observed Count[a]**	**O/E Ratio (95% CI)[b] (PE, 100% RP)**		**O/E Ratio (95% CI)[b] (LB, 50% RP)**	
US	Male	18–29	4.81	0.160	(0.051, 0.379)	**1.270**	**(0.401, 3.009)**
		30–39	10.63	0.285	(0.140, 0.515)	**3.457**	**(1.701, 6.246)**
		40–49	19.11	0.374	(0.226, 0.584)	**6.050**	**(3.649, 9.436)**
		50–64	60.25	0.380	(0.290, 0.489)	**5.888**	**(4.496, 7.575)**
		65–74	25.18	0.236	(0.153, 0.347)	**2.149**	**(1.393, 3.167)**
		≥75	23.95	0.315	(0.202, 0.469)	**4.293**	**(2.749, 6.391)**
	Female	18–29	13.35	0.789	(0.424, 1.340)	**6.907**	**(3.713, 11.730)**
		30–39	13.98	0.610	(0.333, 1.024)	**7.914**	**(4.324, 13.283)**
		40–49	36.46	**1.118**	**(0.785, 1.545)**	**18.084**	**(12.697, 24.984)**
		50–64	61.68	0.580	(0.444, 0.744)	**9.529**	**(7.300, 12.223)**
		65–74	38.62	0.480	(0.340, 0.657)	**5.303**	**(3.764, 7.260)**
		≥75	35.67	0.403	(0.282, 0.559)	**5.016**	**(3.507, 6.955)**
EU	Male	18–29	5.00	**3.062**	**(0.994, 7.146)**	**15.996**	**(5.194, 37.329)**
		30–39	4.00	0.851	(0.232, 2.179)	**2.822**	**(0.769, 7.225)**
		40–49	3.00	0.318	(0.066, 0.930)	0.878	(0.181, 2.565)
		50–64	3.00	0.058	(0.012, 0.169)	0.141	(0.029, 0.411)
		65–74	6.00	0.163	(0.060, 0.355)	0.381	(0.140, 0.830)
		≥75	2.00	0.069	(0.008, 0.248)	0.155	(0.019, 0.560)
	Female	18–29	2.27	**1.613**	**(0.236, 5.434)**	**9.157**	**(1.338, 30.858)**
		30–39	3.17	**1.491**	**(0.326, 4.243)**	**6.256**	**(1.368, 17.805)**
		40–49	3.20	0.570	(0.126, 1.616)	**1.735**	**(0.383, 4.915)**
		50–64	10.32	0.432	(0.210, 0.787)	**1.152**	**(0.560, 2.100)**
		65–74	3.02	0.120	(0.025, 0.351)	0.292	(0.061, 0.851)
		≥75	2.01	0.060	(0.007, 0.215)	0.134	(0.016, 0.484)

Key: CI=Confidence Interval; EU-European Union; LB=Lower Bound; O/E=Observed versus Expected; PE=Point Estimate; RP=Reporting Percentage; US=United States.

a: Counts included cases with events of interest that occurred within the risk window, and cases where time-to-onset was 0 or not reported.

b: Poisson exact confidence interval (95% CI).

A review of the results for the US and EU broad analysis (applying a 100% reporting percentage and point estimate incident rate) showed an O/E ratio of >1 in the US for females in the 40-to-49-year age group only. In the EU, the O/E ratio was >1 for males in the 18-to-29-year age group and for females in the 18 to 29, 30-to-39-year age groups. A sensitivity analysis (applying a 50% reporting percentage and lower bound incident rate) showed an O/E ratio of >1 in the US for both males and females across all age-groups. In the EU, the O/E ratio was >1 for the male:18 to 29, 30 to 39, and female:18 to 29, 30 to 39, 40 to 49 and 50-to-64-year age groups. A restricted O/E analysis was performed (limited to cases with EOI that occurred within the risk window only). Results of the restricted analysis are presented in Table 139.

Table 139: Restricted O/E Analysis Results (Cerebrovascular Events: Haemorrhagic)

O/E Analysis						Sensitivity Analysis	
Region	**Sex**	**Age Range (Years)**	**Observed Count[a]**	**O/E Ratio (95% CI)[b] (PE, 100% RP)**		**O/E Ratio (95% CI)[b] (LB, 50% RP)**	
US	Male	18–29	0.54	0.018	(0.000, 0.158)	0.143	(0.000, 1.254)
		30–39	8.49	0.228	(0.101, 0.440)	**2.761**	**(1.228, 5.337)**
		40–49	14.63	0.286	(0.159, 0.475)	**4.632**	**(2.571, 7.687)**
		50–64	48.46	0.306	(0.226, 0.405)	**4.736**	**(3.497, 6.271)**
		65–74	22.91	0.214	(0.136, 0.322)	**1.955**	**(1.238, 2.936)**
		≥75	20.28	0.267	(0.164, 0.411)	**3.635**	**(2.229, 5.598)**
	Female	18–29	8.11	0.479	(0.208, 0.941)	**4.196**	**(1.824, 8.231)**
		30–39	11.14	0.486	(0.244, 0.867)	**6.306**	**(3.164, 11.243)**
		40–49	25.17	0.772	(0.500, 1.138)	**12.484**	**(8.092, 18.405)**
		50–64	46.34	0.436	(0.319, 0.580)	**7.159**	**(5.248, 9.539)**
		65–74	29.78	0.370	(0.249, 0.529)	**4.089**	**(2.754, 5.845)**
		≥75	28.08	0.317	(0.211, 0.459)	**3.949**	**(2.626, 5.705)**
EU	Male	18–29	2.00	**1.225**	**(0.148, 4.425)**	**6.398**	**(0.775, 23.113)**
		30–39	3.00	0.638	(0.132, 1.865)	**2.116**	**(0.436, 6.185)**
	Female	18–29	2.00	**1.421**	**(0.172, 5.132)**	**8.068**	**(0.977, 29.144)**
		30–39	3.00	**1.411**	**(0.291, 4.123)**	**5.921**	**(1.221, 17.303)**
		40–49	2.00	0.357	(0.043, 1.288)	**1.084**	**(0.131, 3.916)**
		50–64	7.00	0.293	(0.118, 0.604)	0.782	(0.314, 1.611)

Key: CI=Confidence Interval; EU=European Union; LB=Lower Bound; O/E=Observed versus Expected; PE=Point Estimate; RP=Reporting Percentage; US=United States.

a: Counts included cases with events of interest with known time-to-onset that occurred within the risk window only.

b: Poisson exact confidence interval (95% CI).

A review of the results for the restricted analysis (applying a 100% reporting percentage and point estimate incident rate) and a sensitivity analysis (applying a 50% reporting percentage and lower bound incident rate) showed an O/E ratio of <1 for both males and females across all age groups in the US. In the EU, the O/E ratio was >1 for the male: 18 to 29, and female:18 to 29, 30-to-39-year age groups only. A sensitivity analysis (applying a 50% reporting percentage and lower bound incident rate) showed an O/E ratio of >1 in the US and EU for males and females in all age groups with the exception of the US male 18-29 and the EU female 50-to-64-year age groups.

Cerebrovascular events-Non-haemorrhagic

Results of the broad O/E and sensitivity analysis for cerebrovascular events (Non-haemorrhagic) are presented in Table 140.

Table 140: Broad O/E Analysis Results (Cerebrovascular Events: Non-haemorrhagic)

O/E Analysis						Sensitivity Analysis	
Region	**Sex**	**Age Range (Years)**	**Observed Count[a]**	**O/E Ratio (95% CI)[b] (PE, 100% RP)**		**O/E Ratio (95% CI)[b] (LB, 50% RP)**	
US	Male	18–29	6.86	0.291	(0.116, 0.603)	**3.193**	**(1.269, 6.625)**
		30–39	12.68	0.181	(0.095, 0.311)	**2.966**	**(1.565, 5.105)**

Table 140: Broad O/E Analysis Results (Cerebrovascular Events: Non-haemorrhagic)

O/E Analysis						Sensitivity Analysis	
Region	Sex	Age Range (Years)	Observed Count[a]	O/E Ratio (95% CI)[b] (PE, 100% RP)		O/E Ratio (95% CI)[b] (LB, 50% RP)	
		40–49	22.17	0.181	(0.114, 0.273)	**3.218**	**(2.021, 4.865)**
		50–64	81.39	0.171	(0.136, 0.212)	**3.157**	**(2.509, 3.922)**
		65–74	29.23	0.084	(0.057, 0.121)	0.949	(0.637, 1.361)
		≥75	30.98	0.134	(0.091, 0.191)	**1.901**	**(1.291, 2.698)**
	Female	18–29	12.33	0.521	(0.272, 0.903)	**6.865**	**(3.584, 11.905)**
		30–39	19.23	0.351	(0.212, 0.547)	**7.344**	**(4.437, 11.438)**
		40–49	43.90	0.482	(0.350, 0.647)	**11.449**	**(8.315, 15.375)**
		50–64	75.63	0.222	(0.175, 0.278)	**6.405**	**(5.044, 8.022)**
		65–74	44.86	0.158	(0.115, 0.211)	**2.169**	**(1.581, 2.903)**
		≥75	50.37	0.161	(0.119, 0.211)	**2.015**	**(1.498, 2.654)**
EU	Male	18–29	3.56	0.617	(0.151, 1.665)	**2.114**	**(0.519, 5.700)**
		30–39	5.50	0.566	(0.196, 1.273)	**1.611**	**(0.559, 3.624)**
		40–49	9.65	0.268	(0.127, 0.499)	0.633	(0.299, 1.177)
		50–64	17.51	0.067	(0.039, 0.106)	0.146	(0.086, 0.232)
		65–74	7.56	0.037	(0.015, 0.073)	0.078	(0.033, 0.157)
		≥75	5.29	0.031	(0.011, 0.072)	0.066	(0.022, 0.151)
	Female	18–29	4.33	0.845	(0.246, 2.091)	**2.937**	**(0.855, 7.270)**
		30–39	2.42	0.249	(0.040, 0.812)	0.705	(0.112, 2.298)
		40–49	3.48	0.153	(0.037, 0.418)	0.377	(0.091, 1.028)
		50–64	22.98	0.174	(0.111, 0.262)	0.394	(0.250, 0.592)
		65–74	5.42	0.036	(0.013, 0.082)	0.079	(0.027, 0.178)
		≥75	1.23	0.005	(0.000, 0.026)	0.011	(0.001, 0.054)

Key: CI=Confidence Interval; EU-European Union; LB=Lower Bound; O/E=Observed versus Expected; PE=Point Estimate; RP=Reporting Percentage; US=United States.

a: Counts included cases with events of interest that occurred within the risk window, and cases where time-to-onset was 0 or not reported.

b: Poisson exact confidence interval (95% CI).

A review of the results for the US and EU broad analysis (applying a 100% reporting percentage and point estimate incident rate) showed an O/E ratio of <1 in the US and EU for both males and females across all age-groups. A sensitivity analysis (applying a 50% reporting percentage and lower bound incident rate) showed an O/E ratio of >1 in the US for both sexes and all age groups except makes 65to 74 years. In the EU, the O/E ratio was >1 for the male: 18 to 29, 30 to 39 and female 18-to-29-year age groups only.

A restricted O/E analysis was performed (limited to cases with EOI that occurred within the risk window only). Results of the restricted analysis are presented in Table 141.

Table 141: Restricted O/E Analysis Results–Cerebrovascular Events (Non-haemorrhagic)

O/E Analysis						Sensitivity Analysis	
Region	Sex	Age Range (Years)	Observed Count[a]	O/E Ratio (95% CI)[b] (PE, 100% RP)		O/E Ratio (95% CI)[b] (LB, 50% RP)	
		≥75	22.21	0.096	(0.061, 0.146)	**1.363**	**(0.856, 2.059)**
	Female	18–29	7.46	0.315	(0.131, 0.635)	**4.154**	**(1.729, 8.375)**
		30–39	13.58	0.248	(0.134, 0.419)	**5.186**	**(2.805, 8.769)**
		40–49	34.67	0.380	(0.264, 0.530)	**9.042**	**(6.286, 12.594)**
		50–64	55.37	0.162	(0.123, 0.211)	**4.689**	**(3.536, 6.099)**
		65–74	34.21	0.120	(0.083, 0.168)	**1.654**	**(1.147, 2.309)**
		≥75	42.32	0.135	(0.097, 0.182)	**1.693**	**(1.222, 2.286)**
EU	Male	18–29	2.27	0.394	(0.058, 1.327)	**1.348**	**(0.197, 4.542)**
		30–39	4.24	0.437	(0.125, 1.090)	**1.242**	**(0.355, 3.102)**
	Female	18–29	3.00	0.309	(0.064, 0.904)	0.874	(0.180, 2.556)

Key: CI=Confidence Interval; EU-European Union; LB=Lower Bound; O/E=Observed versus Expected; PE=Point Estimate; RP=Reporting Percentage; US=United States.

a: Counts included cases with events of interest with known time-to-onset that occurred within the risk window only.

b: Poisson exact confidence interval (95% CI).

A review of the results for the restricted analysis (applying a 100% reporting percentage and point estimate incident rate) and a sensitivity analysis (applying a 50% reporting percentage and lower bound incident rate) showed an O/E ratio of <1 for both males and females across all age groups. A sensitivity analysis (applying a 50% reporting percentage and lower bound incident rate) showed an O/E ratio of >1 in the US and EU for males and females in all age groups with the exception of the US male 18 to 29 and the EU female 18- to 29-year-old age groups. The RWD analyses did not identify any increased risk of ischaemic stroke (non-haemorrhagic) or haemorrhagic stroke following vaccination with the Ad26.COV2.S

vaccine. Individual case safety report (ICSR) literature cases received during the reporting period were reviewed and no information was identified that would the information on cerebrovascular events.

MAH conclusion The review of the data showed that the majority of the cases were reported in patients with significant risk factors, including advanced age. Many cases were insufficiently documented to allow meaningful causality assessment or did not provide evidence of a cerebrovascular event. Altogether, based on the available data received during this reporting period, there is insufficient evidence to establish a clear causal association between cerebrovascular events and the Ad26.COV2.S vaccine. A higher-than-expected reporting of cerebrovascular events (haemorrhagic and non-haemorrhagic) was observed in the US and EU in the different age groups as detailed above. The increased reporting could be due to multiple factors including reports of cases of thrombosis and thrombocytopenia syndrome, which is now identified as an ADR for Ad26.COV2.S.

Rapporteur assessment comment: During this reporting period, 847 cases reporting cerebrovascular events were retrieved from post-marketing sources. Of these, a total of 1,171 EOI (1,169 serious, 2 nonserious). The age range was 17 to 103 years. Three-hundred seventy-seven cases were reported without risk factors; 76 of these pertained to elderly patients older than 65 years of age. Of the remaining 301 cases without reported risk factors and referring to patients below the age of 65, 74 concerned subjects 40 years or younger. Of these, 8 were reported as fatal cases between 23 and 37 years of age. Three of these cases were indicative of TTS. In 4 there was not enough information to assess causality, and in one case no information was available. Altogether, based on the available data received during this reporting period, there is insufficient evidence to establish a clear causal association between cerebrovascular events and the Ad26.COV2.S vaccine.

Cerebrovascular events mainly focusing on VTE, in subjects vaccinated with Ad26.COV2.S were assessed in depth in the procedure EMEA/H/C/005737/MEA/032 (procedure after cutoff for this reporting period). Cerebrovascular events have been focused on in the MSSRs (EMEA/H/C/005737/MEA/014.2; EMEA/H/C/005737/MEA/014.4; EMEA/H/C/005737/MEA/014.7). In the MSSR 014.4, the MAH was requested to continuously discuss cerebrovascular events in upcoming MSSRs and PSURs; any new case reports in vaccinees 40 years or below should be provided in detail, including any additional information received on these cases and it is still highly relevant for upcoming PSURs and MSSRs. As described in MEA 14.4, it is also important to continue differentiate between hemorrhagic and non-hemorrhagic events.

Disseminated Intravascular Coagulation

Although the PBRER reporting period is from 25 February 2021 to 24 August 2021, the O/E analysis covers the period of 25 February 2021 to 31 August 2021.

Results/Discussion

During this reporting period, 14 (13 medically confirmed and 1 medically unconfirmed) cases reporting DIC were identified; All serious and from post-marketing sources

most frequently from the US (n=10). Five cases concerned males and 9 females. The age range was 37 to 68 years.

The mean and median TTO was 16.4 and 12 days, respectively. Where reported (n=10), the outcome was reported as not resolving (n=4), fatal (all DIC n=3), and resolving (n=3).

O/E Analysis

Results of the broad O/E and sensitivity analysis are presented in Table 144.

Table 144: Broad O/E Analysis Results–Disseminated Intravascular Coagulation

Region	Age Range (Years)	Observed Count[a]	O/E Analysis O/E ratio (95% CI)[b] (PE, 100% RP)		Sensitivity Analysis O/E ratio (95% CI)[b] (LB, 50% RP)	
US	18 to 59	6.00	0.045	(0.016, 0.098)	0.090	(0.033, 0.195)
	≥60	2.00	0.017	(0.002, 0.063)	0.035	(0.004, 0.125)
EU	18 to 59	3.00	0.024	(0.005, 0.069)	0.048	(0.010, 0.139)
	≥60	0.00	0.000	(0.000, 0.039)	0.000	(0.000, 0.078)

Key: CI=Confidence Interval; EU-European Union; LB=Lower Bound; O/E=Observed versus Expected; PE=Point Estimate; RP=Reporting Percentage; US=United States.

a: Counts included cases with events of interest that occurred within the risk window, and cases where time-to-onset was 0 or not reported.

b: Poisson exact confidence interval (95% CI).

MAHs Conclusion Based on the review of available data no new safety information was identified during the reporting period for disseminated intravascular coagulation.

Rapporteur assessment comment:

No new safety concern is detected here; DIC has been repeatedly assessed in MSSRs

Thromboembolic and Thrombotic Events Without Thrombocytopenia

VTE is listed as an Important Potential Risk for Ad26.COV2.S following an imbalance of VTE cases, particularly deep vein thrombosis and pulmonary embolism, in the interim analysis of study COV3001.

PRAC rapporteur comments: Thromboembolism has been evaluated in depth in a specific MEA (EMEA/H/C/005737/MEA/032); as well as in the MSSRs (EMEA/H/C/005737/MEA/014.1-07). MEA 032 resulted in updates of the PI (Section 4.4 and 4.8 of the SmPC and the PIL accordingly). No new information has been provided in this PSUR; particularly since this assessment predominantly was undertaken after the DLP of the PSUR. Therefore, no additional details are provided below for the data included in the PSUR.

2.3.4.6. Hepatic Disorders

Acute Hepatic Failure

Although the PBRER reporting period is from 25 February 2021 to 24 August 2021, the O/E analysis covers the period of 25 February 2021 to 31 August 2021.

Results/Discussion

During this reporting period, 30 (17 medically confirmed and 13 medically unconfirmed) cases reporting acute hepatic failure were identified. Of these 30 cases, 29 were serious and 1 was nonserious reporting a total of 34 events (29 serious, 5 nonserious). See Table 152 below. A single case may report more than 1 EOI.

Table 152: Frequency of MedDRA PTs of Interest Involving the Use of Ad26.COV2.S and Reporting Acute Hepatic Failure (Events=34)

MedDRA PTs	Number of Events	
	Serious	Nonserious
Hepatic steatosis	4	2
Liver injury	5	0
Hepatic failure	5	0
Acute hepatic failure	4	0
Liver disorder	1	2
Oesophageal varices haemorrhage	2	0
Hepatic lesion	1	1

Table 152: Frequency of MedDRA PTs of Interest Involving the Use of Ad26.COV2.S and Reporting Acute Hepatic Failure (Events=34)

MedDRA PTs	Number of Events	
	Serious	Nonserious
Ascites	2	0
Portal vein dilatation	1	0
Nonalcoholic fatty liver disease	1	0
Hepatic encephalopathy	1	0
Asterixis	1	0
Liver transplant	1	0
Total	**29**	**5**

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term.

Placebo-controlled Studies

There were no cases retrieved from the search of the Company global safety database.

Open-label Studies [VAC31518COV3012 (Sisonke); and VAC31518COV4007 (Brazil Early Access)]

During this reporting period, 2 cases reporting events related to acute hepatic failure from open-label studies were identified (VAC31518COV3012); reporting 2 serious EOIs. Both concerned males one age as 30-year-old and for one the age was not reported. The EOIs included non-alcoholic fatty liver disease (n=1) and oesophageal varices haemorrhage (n=1). The mean and median TTO was 12.5 days. The outcome of the EOIs was reported as fatal (n=1) or resolving (n=1). The event with a fatal outcome was oesophageal varices haemorrhage, the patient did not have risk factors in medical history for the EOI, there was missing information in the case with regards to the complete clinical course of the EOI up until the fatal outcome, including information on any pre-exiting oesophageal varices and their status, which makes the medical assessment difficult. The Company/reporter causality were assessed as not related for both cases.

Post-marketing Sources (Including Spontaneous and Solicited Cases)

During this reporting period, 28 cases reporting acute hepatic failure were retrieved; 32 EOIs (27 serious, 5 nonserious); most frequently reported from the US (n=24). Ten cases concerned males, 15 females, and 3 did not report sex. The age range was 27 to 78 years. The EOIs included hepatic steatosis (n=6), liver injury (n=5), and hepatic failure (n=5), acute hepatic failure (n=4), liver disorder (n=3), ascites (n=2), and hepatic lesion (n=2), and 1 each of oesophageal varices haemorrhage, hepatic encephalopathy, portal vein dilatation, asterixis, and liver transplant.

Assessment of the 28 cases was performed for acute liver injury per: Bernuau System- >50% decrease in Factor II or V with HE; O' Grady System- Severe liver injury with HE without prior liver disease; IASL System- Severe liver Dysfunction with HE within 4 weeks without prior liver disease; Japanese System- INR ≥1.5 or prothrombin time≤40% within 8 weeks of symptoms without prior liver disease. No cases met case definition as laboratory values were not provided. The mean and median TTO was 17.8 days and 14 days, respectively. Of the 32 EOIs, 9 were reported outside the risk window of 14 days. In 16 of the 28 cases, the lack of various clinical details precluded a meaningful causal assessment between the vaccine and the reported EOIs. The remaining 12 cases were confounded by concurrent active COVID-19 infection, staphylococcal infection, alcoholic hepatitis, acetaminophen toxicity, hospitalisation for liver

transplant with postoperative recurrence of portal thrombosis, underlying conditions of hypertension, diabetes mellitus, alcohol abuse, non-alcoholic steatohepatitis, cirrhosis with recent decompensation, portal hypertension, hepatitis B, alcoholic cirrhosis, obesity, stage IIIa rectal cancer, chronic active hepatitis C, esophageal varices, concomitant medications of hydrocodone/paracetamol and paracetamol. Where reported (n=20), the outcome was reported as not resolved (n=8), resolved (n=7), fatal (n=4), and resolving (n=1). The events with a fatal outcome were hepatic steatosis (n=2), hepatic failure, and esophageal varices haemorrhage (n=1 each). From the 4 fatal outcome cases, 3 were confounded by relevant medical history (concurrent liver disease, hepatitis C, alcohol abuse, and cirrhosis of the liver). In the last fatal case, there was no clear aetiology for encephalopathy, and thrombocytopenia was identified with underlying concurrent urinary tract infection (no definite sepsis). Considering insufficient information about various factors, the relationship to vaccination was not assessable.

O/E Analysis

Results of the broad O/E and sensitivity analysis are presented in Table 153.

Table 153: Broad O/E Analysis Results (Acute Hepatic Failure)

O/E Analysis					Sensitivity Analysis	
Region	Age Range (Years)	Observed Count[a]	O/E ratio (95% CI)[b] (PE, 100% RP)		O/E ratio (95% CI)[b] (LB, 50% RP)	
US	18 to 59	12.57	5.704	(3.000–9.841)	11.408	(6.000–19.682)
	≥60	5.38	6.874	(2.349–15.589)	13.748	(4.699–31.178)
EU	18 to 59	1.00	0.015	(0.000-0.086)	0.038	(0.001-0.209)
	≥60	1.00	0.023	(0.001-0.130)	0.055	(0.001-0.304)

Key: CI=Confidence Interval; EU=European Union; LB=Lower Bound; O/E=Observed Versus Expected; PE=Point Estimate; RP=Reporting Percentage; US=United States.
a: Counts included cases with events of interest that occurred within the risk window, and cases where time-to onset was 0 or not reported.
b: Poisson exact confidence interval (95% CI).

Results of the restricted analysis are presented in Table 154.

Table 154: Restricted O/E Analysis Results (Acute Hepatic Failure)

O/E Analysis					Sensitivity Analysis	
Region	Age Range (Years)	Observed Count[a]	O/E ratio (95% CI)[b] (PE, 100% RP)		O/E ratio (95% CI)[b] (LB, 50% RP)	
US	18 to 59	7.00	3.177	(1.277–6.545)	6.353	(2.554-13.090)
	≥60	2.00	2.555	(0.309–9.231)	2.619	(0.619-18.462)

Key: CI=Confidence Interval; LB=Lower Bound; O/E=Observed versus Expected; PE=Point Estimate; RP=Reporting Percentage; US=United States.
a: Counts included cases with events of interest with known time-to-onset that occurred within the risk window only.
b: Poisson exact confidence interval (95%CI).

A review of the results for the restricted analysis (applying a 100% reporting percentage and point estimate Incident Rate) and a sensitivity analysis (applying a 50% reporting percentage and lower bound incident rate) showed an O/E ratio of >1 for both age groups in the US.

MAH Conclusion Based on the review of available data, no new safety information was identified during the reporting period for acute hepatic failure. Although the O/E analysis showed an O/E ratio of >1 in the US, the cumulative review of the individual cases did not identify sufficient evidence to support a causal association between acute hepatic failure and Ad26.COV2.S. The MAH will continue monitoring this topic via routine PV activities.

Rapporteur assessment comment:

No new safety concern is detected here.

2.3.4.7. Renal Disorders

Acute Kidney Failure

Although the PBRER reporting period is from 25 February 2021 to 24 August 2021, the O/E analysis covers the period of 25 February 2021 to 31 August 2021.

Results/Discussion

During this reporting period, 59 (49 medically confirmed and 10 medically unconfirmed) cases reporting acute kidney failure were identified. All 59 cases were serious and reported a total of 69 serious events. See Table 156 below. A single case may contain more than 1 EOI.

Table 156: Frequency of MedDRA PTs of Interest Involving the Use of Ad26.COV2.S and Reporting Acute Kidney Failure (Events=69)

MedDRA PTs	Number of Serious Events
Acute kidney injury	35
Renal failure	11
Renal impairment	7
Haemodialysis	6
Dialysis	5
Anuria	3
Continuous haemodiafiltration	1
Oliguria	1
Total	**69**

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term.

Placebo-controlled Studies

During this reporting period, 7 cases reporting acute kidney failure were retrieved from placebo-controlled studies; VAC31518COV3001 (n=6) and VAC31518COV3009 (n=1); and reported 7 serious EOIs. These 7 cases were reported from the US (n=5), Argentina (n=1), and Colombia (n=1), 2 in females, 5 males with an age range of 39 to 78 years. The mean and median TTO was 87.8 days and 60 days, respectively. The outcome for the 7 events were reported as resolved (n=6) and not resolved (n=1). EOI causality for both Company/reporter was assessed as not related.

Open-label Studies [VAC31518COV3012 (Sisonke); and VAC31518COV4007 (Brazil Early Access)]

During this reporting period, 2 cases reporting acute kidney failure were retrieved from open-label studies (VAC31518COV3012); 2 serious EOIs, and concerned a 32-year-old male and 29-year-old female. The EOI included acute kidney injury and renal failure. The mean and median TTO was 26 days. The outcome for the 2 events were reported as fatal (n=1) and not resolved (n=1). In 1 case, the Company causality was assessed as not related and reporter causality was not reported. In the remaining case, the Company causality was assessed as not related and the reporter causality as possibly related.

Post-marketing Sources (Including Spontaneous and Solicited Cases)

During this reporting period, 50 cases reporting acute kidney failure; 60 serious EOIs; most frequently from the US (n=41). 26 concerned females, 21 males, and 3 did not report sex. The age range was 20 to 94 years. The EOI included acute kidney injury (n=27), renal failure (n=10), renal impairment (n=7), haemodialysis (n=6), dialysis (n=5), anuria (n=3) and 1 each of continuous hemodiafiltration and oliguria. The mean and median TTO was 19.4 days and 16 days, respectively. Where reported (n=46), the outcome was reported as not resolved (n=23), fatal (n=14), resolved (n=7), and resolving (n=2). There were 10 fatal cases with 14 fatal EOI. The events with a fatal outcome were acute kidney injury (n=6), 2 each of dialysis and haemodialysis, and 1 each of renal impairment, renal failure, continuous

hemodiafiltration, and oliguria. TTO in these cases ranged from 2 to 33 days (median=16 days). Most these cases were confounded (n=8) by the patients' medical history and/or concurrent disease, which included underlying diabetes mellitus (n=3), hypertension (n=4), underlying congestive heart failure (n=1), chronic kidney disease (n=1), morbid obesity (n=1), idiopathic CLS with monoclonal gammopathy (n=1), ethyl alcohol abuse (n=1), and concurrent COVID-19 infection (n=3 cases), urinary tract infection (n=1), diabetic ketoacidosis (n=1), gemcitabine and cisplatin use for metastatic intrahepatic cholangiocarcinoma (n=1) and hospitalisation for liver transplant with postoperative thrombosis, including renal vein thrombosis (n=1).

O/E Analysis

Results of the broad O/E and sensitivity analysis are presented in Table 157.

Table 157: Broad O/E Analysis Results–Acute Kidney Failure

	O/E Analysis				Sensitivity Analysis	
Region	**Age Range (Years)**	**Observed Count[a]**	**O/E ratio (95% CI)[b] (PE, 100% RP)**		**O/E ratio (95% CI)[b] (LB, 50% RP)**	
US	18-59	10.29	0.123	(0.060-0.224)	0.263	(0.128-0.480)
	≥60	17.69	0.595	(0.351-0.944)	**1.275**	**(0.752-2.023)**
EU	18-59	5.00	0.038	(0.012-0.089)	0.087	(0.028-0.204)
	≥60	0.00	0.000	(0.000-0.007)	0.000	(0.000-0.014)

Key: CI=Confidence Interval; EU=European Union; LB=Lower Bound; O/E=Observed versus Expected; PE=Point Estimate; RP=Reporting Percentage; US=United States.
a: Counts included cases with events of interest that occurred within the risk window, and cases where time-to-onset was 0 or not reported.
b: Poisson exact confidence interval (95% CI).

A restricted O/E analysis was performed for the US for the ≥ 60-year-old age group (limited to cases with EOI that occurred within the risk window only); Table 158.

Table 158: Restricted O/E Analysis Results–Acute Kidney Failure

	O/E Analysis				Sensitivity Analysis	
Region	**Age Range (Years)**	**Observed Count[a]**	**O/E ratio (95% CI)[b] (PE, 100% RP)**		**O/E ratio (95% CI)[b] (LB, 50% RP)**	
US	≥60	8.00	0.269	(0.116, 0.530)	0.577	(0.249, 1.136)

Key: CI=Confidence Interval; LB=Lower Bound; O/E=Observed versus Expected; PE=Point Estimate; RP=Reporting Percentage; US=United States.
a: Counts included cases with events of interest with known time-to-onset that occurred within the risk window only.
b: Poisson exact confidence interval (95% CI).

MAH conclusion Based on the review of the available data, no new safety information was identified during the reporting period for acute kidney failure. An assessment of aggregate data and O/E analysis did not highlight a safety concern. Altogether, at present, there is insufficient evidence to establish a causal association between Ad26.COV2.S and acute kidney failure.

Rapporteur assessment comment:

No new safety concern is detected here.

2.3.4.8. Death

During this reporting period, 684 (427 medically confirmed and 257 medically unconfirmed) cases reporting 1,874 events with a fatal outcome were identified. Of these 684 cases, 80 were from placebo-controlled studies, 64 from open-label studies, and 540 from post-marketing sources (including spontaneous and solicited cases). The frequency distribution of top 10 fatal MedDRA PTs reported in these 684cases is presented in Table 160 below. A single case may report more than 1 fatal EOI.

Table 160: Frequency Distribution of Top 10 Reported Fatal MedDRA PTs Involving the Use of Ad26.COV2.S (n=1,874)

MedDRA PTs	Number of Fatal Events[a]
Death	301
COVID-19	81
Thrombosis	48
Myocardial infarction	37
Pulmonary embolism	34
Cerebrovascular accident	31
Cardiac arrest	30
Dyspnoea	29
Pyrexia	24
Cerebral haemorrhage	23

Key: COVID-19=Coronavirus disease of 2019; MedDRA=Medical Dictionary for Regulatory Activities; n=Number of Fatal Events; PT=Preferred Term.
a: A single case may report more than 1 fatal MedDRA Preferred Terms.

Reporting Rate and Reporting Ratio

The reporting rate (RR) of all the cases was 49.99 per 100 patient treatment years and the RR of the fatal cases was 0.59 per 100 patient treatment years. The ratio of the fatal cases was 0.01.

The RR of all events was 201.33 per 100 patient treatment years and the RR of the fatal events was 1.86 per 100 patient treatment years. The ratio of the fatal events was 0.009. Individual case safety report literature cases received during the reporting period were reviewed and upon review of the 6 cases, no information was identified that would raise a new specific safety concern.

MAH conclusion Based on the review of the available data, the analysis of fatal events has not raised any new safety concerns and the Company will continue to monitor the serious, life threatening, and fatal cases.

Rapporteur assessment comment:

No new safety concern is detected here.

2.4. Characterisation of risks

2.4.1. Characterisation of Important Potential Risks

See sections above.

3. Benefit evaluation

Benefit of this vaccine was demonstrated in adults based on the primary efficacy analysis of the pivotal study COV3001, including 19,630 participants who received Ad26.COV2.S and 19,691 participants who received placebo. Vaccine efficacy (adjusted 95% CI) for the co-primary endpoints against molecularly confirmed moderate to severe/critical COVID-19 in participants who were seronegative at time of vaccination was 66.9% (59.03; 73.40) when considering cases from at least 14 days after vaccination and 66.1% (55.01; 74.80) when considering cases from at least 28 days after vaccination. Consistent efficacy was shown across age groups.

Vaccine efficacy (adjusted 95% CI) against severe/critical COVID-19 occurring at least 14 days after a single Ad26.COV2.S dose was 76.7% (54.56; 89.09) and increased to 85.4% (54.15; 96.90) for severe/critical COVID-19 occurring at least 28 days after a single Ad26.COV2.S dose. Vaccine efficacy against severe/critical COVID-19 was consistently high across age groups in adults, regions and countries.

There are no new efficacy data occurring during the PSUR period.

4. Benefit-risk balance

Ad26.COV2.S (COVID-19 Vaccine Janssen) has been proven to be efficacious against Ad26.COV2.S.

Several AESIs including TTS, venous thromboembolism, ITP, GBS, transverse myelitis, CLS and vasculitis have been shown to occur very seldomly or with unknown frequency with the vaccine, which have been reflected in the SmPC during or after the reporting period of the current PSUR. Additionally, uncertainties remain open for the following items and have to be further followed up in the upcoming MSSRs and PSURs, i.e MIS, encephalitis/ADEM, cerebrovascular events and myocarditis/pericarditis.

Based on the hitherto available data, the **benefit/risk balance** for COVID-19 vaccine Janssen remains positive.

5. Rapporteur Request for supplementary information

1. **Serious Hypertension**: Eighteen serious cases of hypertension (on a total of 30 cases of hypertension) have been reported as of 20 October 2021in France. The MAH is requested to present a cumulative review focused on serious hypertension, including details of any underlying condition(s) (including COVID-19), time to onset, duration and outcome, together with an assessment of the causal relationship with the vaccine and a discussion on the need to update the product information, if applicable.
2. The MAH has summarized 6 cases of new onset of **autoimmune hepatitis** without presenting the cases in depth. The MAH is requested to complete the cases with narratives and present a thorough evaluation of these cases.

6. MAH responses to Request for supplementary information

Serious Hypertension

Epidemiology of Disease/Adverse Event

As per Guidelines of the Task Force for the management of arterial hypertension of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESC), hypertension is defined as an office systolic blood pressure (SBP) of ⩾140 mmHg and/or a diastolic blood pressure (DBP) of ⩾90 mmHg. (Williams 2018)

The global prevalence of hypertension was estimated to be 1.13 billion in 2015, with a prevalence of over 150 million in central and eastern Europe. The overall prevalence of hypertension in adults was approximately 30% to 45%, with a global age-standardised prevalence of 24% and 20% in men and women, respectively, in 2015. This high prevalence of hypertension is consistent across the world, irrespective of income status, ie, in lower, middle, and higher-income countries.

Hypertension becomes progressively more common with advancing age, with a prevalence of >60% in people aged >60 years. (Williams 2018). An estimated 46% of adults with hypertension are unaware that they have the condition. Less than half of adults (42%) with hypertension are diagnosed and treated. Approximately 1 in 5 adults (21%) with hypertension have it under control (Hypertension, 2021).

Hypertension may be primary, which develops as a result of environmental or genetic causes, or secondary, which has multiple aetiologies, including renal, vascular, and endocrine causes. Primary or essential hypertension accounts for 90% to 95% of adult cases, and a small percentage (2% to 10%) is attributable to secondary causes (Williams 2018).

Risk factors for hypertension include, a history of cardiovascular disease, stroke or transient ischaemic attacks, dyslipidaemia, chronic kidney disease, smoking status, diet, alcohol intake, lack of physical activity, history of depression, hypercholesterolaemia, thyroid disease, and diabetes (Unger 2020; Eszter 2019).

Especially severe cases of hypertension, or hypertensive crises, are defined as a blood pressure (BP) of >180/120 mmHg and may be further categorised as hypertensive emergencies or urgencies. Hypertensive emergencies are characterised by evidence of impending or progressive target organ dysfunction, whereas hypertensive urgencies are those situations without progressive target organ dysfunction (Chobanian 2003). The aetiology of acute BP elevations is variable. Noncompliance with antihypertensive therapy, use of sympathomimetics, and thyroid dysfunction are among the many possible causes of hypertensive urgencies. Even anxiety and pain may cause acute elevations in BP (Alley 2021).

Class Effect and Biological Plausibility

Pharmacological Class Effect

For comparison, the product information for other approved COVID-19 vaccines were reviewed for hypertension/increased BP.

- Vaxzevria does not include information regarding hypertension or increased BP within the approved EU SmPC
- Comirnaty lists alterations in BP under anxiety-related reactions in Section 4.4 Special warnings and precautions for use within the approved EU SmPC
- Spikevax does not include information regarding hypertension or increased BP within the approved EU SmPC

Biological Plausibility

Within the published biomedical literature, limited data was identified regarding a potential mechanism of action (MOA) for the development of de novo serious hypertension following the administration of COVID-19 vaccines. Meylan 2021, which reported a cases series of 9 patients presenting with Stage III hypertension within minutes post vaccination speculated that the event could be triggered via stress, pain response, or the white coat effect. The authors noted however that the relatively low heart rate observed in the patients (median 73 bmp) would make the stress, pain or white coat effect less likely. A proposed alternative theoryincludeda reaction to adjuvants, such as PEG or tromethamine, although Bouhanick 2021 deemed this unlikely due to the short time to onset (TTO) and low dosage of adjuvants administered. The authors suggested an interaction with the renin-angiotensin system possibly accounting for tardive hypertension. Moreover, Sanidas 2021 and Zappa 2021 acknowledged that the pathophysiological link between COVID-19 vaccines and an increase in BP remains unclear. SARS coronavirus uses angiotensin- converting enzyme 2 (ACE2) as receptor for Spike protein to gain cell entry. Regarding the mRNA vaccines, it was noted that mRNA encodes the Spike protein of SARS-CoV-2. After translation into protein in cells, the Spike protein congregates into the cytoplasm, migrates to cell

surfaces, and is subsequently recognised by the immune system, causing the recombinant Spike-producing cells to be destroyed. Spike protein was proposed to subsequently circulate in the blood and interact with ACE2 receptors resulting in the internalisation and potential degradation of the receptors (cells expressing receptors) (Sanidas 2021).

It is important to note the functions of ACE2, while hypothesising the potential impact of S-antigen expression by vaccines. ACE2, a homologue of ACE (angiotensin-converting enzyme), is a type I transmembrane glycoprotein which cleaves amino acid phenyl alanine and has an opposing action to the ACE (Kuba 2013). While ACE increases the formation of angiotensin II (which is the main18 effector of the renin-angiotensin system and causes sodium and water retention), aldosterone release from adrenal and overall increase in BP, ACE2 helps conversion of angiotensin I into angiotensin (1-9) as well as conversion of angiotensin II into angiotensin (1-7) (Donoghue, 2000). Angiotensin 1-7 and angiotensin 1-9 both have broadly vasoprotective and anti-inflammatory effects (Gonzalez 2018; Santos2019; Marquez 2019).

It has been theorised that binding of released Spike protein to ACE2 and the consequent imbalance between angiotensin II (overactivity) and angiotensin 1-7/ 1-9 (deficiency) may play a role in the pathogenesis of hypertension post-vaccination (Sanidas 2021). However, there is currently no evidence in the literature that ACE 2 levels are affected by replication deficient adenoviral vector mediated expression of the S antigen (Spike protein).

Product Exposure

Phase 3 randomized, placebo controlled Clinical Trial Exposure

As of 31 December 2021, during the entire double blind phase of the study VAC31518COV3001, there were 21,894 subjects exposed to Ad26.COV2.S vaccine while 21,882 subjects were exposed to the placebo. During the entire double blind phase of the study VAC31518COV3009, there were 15,705 subjects exposed to Ad26.COV2.S vaccine while 15,588 subjects were exposed to placebo.

Post-marketing Exposure

Estimates of exposure are based on the number of delivered doses reported from LYNX Finance and administered doses reported from Centers for Disease Control and Prevention (CDC 2021) for the United States (US), European Centre for Disease Prevention and Control (ECDC 2021) for European Economic Area (EEA) countries, Korea Disease Control and Prevention Agency (KDCA 2021) for South Korea, and Ministério da Saúde (Ministério da Saúde 2021) for Brazil. Cumulatively, there were 126,191,050 doses distributed worldwide in addition to 61,266,550 doses donated by the US and EU to various countries, including donations through the GAVI/COVAX agreement. A total of 187,457,600 doses of the Ad26.COV2.S vaccine were distributed worldwide from launch to 30 November 2021. A total of 40,826,412 doses of Ad26.COV2.S vaccine were administered worldwide from launch to 30 November 2021.

METHODS AND ANALYSIS

Clinical Trial Data

Serious cases from the large phase 3 COVID-19 vaccine clinical trials VAC31518COV3001 and VAC31518COV3009 with serious events coded to the MedDRA SMQ Hypertension (narrow) were reviewed in detail as part of review of all safety data in the GMS Global Safety Database as of 30 November 2021. In addition, it was checked if there was any imbalance for serious events of interest (EOIs) included in MedDRA SMQ Hypertension (narrow) in these 2 double-blind, placebo-controlled phase 3 studies: Study VAC31518COV3001 (data cutoff: 09 July 2021) and Study VAC31518COV3009 (data cutoff: 25 June 2021).

GMS Global Safety Database

A search of the GMS Global Safety Database was performed for all cases that met the following criteria:

- Janssen COVID-19 vaccine (Ad26.COV2.S) as suspect, or suspect-interacting, drug
- adverse events coded to the MedDRA version 24.1 SMQ Hypertension (narrow)
- medically confirmed cases and not medically confirmed cases
- cases reporting events related to serious hypertension only
- all case types (eg, spontaneous/clinical trial serious adverse events [SAEs]/registry, etc.)
- version of case: highest version in date range
- cases received cumulatively through 30 November 2021; cases that were in workflow at the time of the GMS global safety database search were not captured as part of this search.

Cases from Ad26.COV2.S Company-sponsored clinical trials were included in the search of the GMS global safety database; therefore, there is the potential for duplication of cases between Section 4.1, Review of Clinical Trials and Section 4.2, Review ofCases From GMS Global Safety Database.

- All cases retrieved by the search were reviewed and analysed according to the following methods:

Aggregate review:

Initial aggregate data analysis: the retrieved cases were analysed and stratified by patient demographics (sex, age) and case characteristics (country of origin, indication, Preferred Terms of EOI

Case level review:

Cases were assessed for the presence of key attributes in order to determine if they provided a meaningful level of detail for a case assessment. This included patient demographics, medical history, concomitant medications, laboratory and diagnostic test results, baseline and post-vaccination BP values and clinical course. Cases lacking major components were stratified to the category of limited information.

Grading of the event of hypertension based on reported BP values was performed, according to the ESC ESH Guidelines (Williams, 2018). In cases reporting multiple BP values, the highest value was considered for grading. If the SBP and DBP values fell into 2 separate grading categories, the case was classified into the higher category. Case narratives were assessed for information on baseline and post vaccination BP values. Duration of the EOI was assessed based on time to resolution.

Confounding factors (ie, risk factors, alternate etiologies for hypertension) were evaluated by reviewing medical history data fields, concomitant and co-suspect medication fields, concurrent AE PTs, and the case narrative. As noted in the results section, only a few cases provided baseline or historical BP values. Therefore, it remained unclear whether the reported event was a new onset or reflection of pre-existing disease. Underlying risk factors in a patient's concurrent medical history and concurrent adverse events were captured as confounding factors. Based on aggregate analysis, cases were grouped according to the presence of concurrent events as displayed below. Even though there was a small number of cases documenting pregnancy, these cases were assessed as a separate group due to the importance ofevaluation of the product safety profile in pregnant women.

Grouping was done as follows:

Cases documenting concurrent:

- anxiety
- pregnancy

- thromboembolic, haemorrhagic, or ischaemic events
- Other cases

Considering the large number of cases (hypertension including serious hypertension is one of the most common diseases in the general population), individual cases are not presented in this aggregate review. However, analysis of cases includes granular details regarding the number and percentage of cases with specific confounders or risk factors. Sentinel case: case for which there is strong evidence of a potential association between the vaccine exposure and adverse event without confounding factors.21

Literature

Integrated searches of the major biomedical literature databases were performed cumulatively through 10 December 2021 for reports/articles relating to: 1) hypertension/increased BP and the Janssen COVID-19 vaccine, 2) hypertension/increased BP and all other COVID-19 vaccine. The biomedical literature databases searched included BIOSIS Previews, MEDLINE, Derwent Drug File, and Embase. Only articles relevant to the research question were included in the analysis. Relevant information from these publications is presented in Sections 2.3.2 Biological Plausibility and Section 4.3, Literature.

4. RESULTS

4.1. Review of Clinical Trials

There was no significant imbalance in reporting of hypertension or hypertensive disorders in both studies VAC31518COV3001 and VAC31518COV3009. In study VAC31518COV3001, during the double blind stage, there were 4 subjects in the Ad26.COV2.S group who experienced serious adverse events (SAEs) of hypertension (n=2), hypertensive crisis (n=1) or hypertensive urgency (n=1). In the placebo group, there were 2 subjects who experienced an SAE of hypertension and 1 subject who experienced an SAE of hypertensive encephalopathy. In study VAC31518COV3009, during the double-blind stage, there was 1 subject who experienced the SAE of hypertensive crisis in the Ad26.COV2.S group, and 1 subject who experienced the SAE of essential hypertension in the placebo group. None of the cases from clinical trials VAC31518COV3001 and VAC31518COV3009 reporting SAEs of hypertension were considered related. Most subjects who experienced an SAE of hypertension had a history of hypertension or cardiovascular disease or concomitant diseases of cardiovascular nature. All 5 cases in the Ad26.COV2.S groups involved subjects >45 years of age and documented comorbid/concurrent conditions, including at least 1 of the following risk factors: coronary artery disease, pulmonary embolism, hypercholesterolemia, nicotine dependence/smoking, obesity, asthma, anxiety, congestive heart failure, chronic obstructive pulmonary disease (COPD), myocardial infarction or a medical history of pre-existing hypertension. Outcome was reported as recovered and resolved in all cases within a period of 1 day to 6 days. 4.2. Review of Cases From GMS Global Safety Database

Rapporteur assessment comment:

Clinical studies have not identified significant safety concerns regarding hypertension with the Janssen Covid-19 vaccine.

Aggregate Data Results

The search of the GMS global safety database through 30 November 2021 retrieved 678 cases reporting 693 serious EOIs, which included 10 cases from interventional clinical trials, 12 cases from non-interventional trials, and 656 spontaneous cases. The frequency distribution of EOI and case

characteristics for cases reporting serious hypertension with Ad26.COV2.S are presented in Table 1 and Table 2, respectively.

Table 1: Frequency of the MedDRA Preferred Terms of Interest For Cases Reporting Events Related to Serious Hypertension With the Use of Ad26.COV2.S (n=693)

MedDRA Preferred Term	Number of Events[a]
Blood pressure increased	381
Hypertension	244
Hypertensive crisis	32
Pre-eclampsia	8
Hypertensive urgency	5
Hypertensive emergency	4
Hypertensive heart disease	3
Blood pressure inadequately controlled	2
Eclampsia	2
Gestational hypertension	2
HELLP syndrome	2
Labile hypertension	2
Blood pressure diastolic increased	1
Diastolic hypertension	1
Essential hypertension	1
Hypertensive encephalopathy	1
Malignant hypertension	1
Metabolic syndrome	1
Grand Total	**693**

Key: MedDRA=Medical Dictionary for Regulatory Activities

a: A single case may report more than 1 MedDRA Preferred Term of interest.

Table 2: Characteristics and Demographics of Cases Reporting Serious Hypertension With the Use of Ad26.COV2.S (n=678)

Characteristic		Number of Cases
Source	Spontaneous[a]	656
	Clinical Study (non-interventional, solicited)	12
	Clinical Study (interventional, non-solicted)	10
Patient Sex	Female	372
	Male	296
	NR	10
Patient Age (Years)[b] **Mean: 55.6** **Median: 56** **Range: 18 to 98**	5 to 17	0
	18 to 35	55
	36 to 50	167
	51 to 64	250
	≥65	176
	NR	30
	Child	0
	Adult	474
	Elderly	176
	NR	28
Outcome (Event Level)[c]	Resolved/resolved with sequelae	404
	Fatal	20
	Resolving	64
	Not resolved	126
	NR	79
Country of Origin	Philippines	325
	United States of America	186
	France	27
	Germany	21
	Italy	19
	Romania	11
	Portugal	10
	South Africa	10
	Poland	8
	Greece	7
	Austria	6
	Brazil	5
	Belgium	4
	Czech Republic	4
	Latvia	4
	Spain	4
	Estonia	3
	Lithuania	3
	Colombia	2
	Croatia	2
	Netherlands	2
	Slovenia	2
	Remaining countries[d]	13

Key: n= Number; NR= Not Reported
a: Cases included 1 case from literature source.
b: For cases where age is not reported, reported age category is presented.
c: For the event(s) of interest.
d: Argentina, Bulgaria, Canada, Egypt, Iceland, Ireland, Korea, Republic of, Lao People's Democratic Republic, Morocco, Namibia, Switzerland, Thailand, Zambia.

Most cases referred to adult females. The mean age was 57.5 years, the median age was 58 years, and the age range was 19 to 98 years. Approximately half of the cases (47.9%; 325/678) identified with serious hypertension originated from the Philippines where monitoring of BP is part of the screening process in the COVID-19 vaccination program. During this screening process, it is highly likely that undetected hypertension is diagnosed at the time of vaccination or that any elevation in BP due to anxiety to vaccination is reported. This national program recommends monitoring of BP in vaccine recipients with a history of hypertension, with symptomatic hypertension, and based upon the clinical judgement of the physician on site (Food and Drug administration Philippines, 2021). Therefore, the events in most of these cases may be more accurately categorised as solicited and reported in a patient population with pre-existing hypertension. Hence these cases from the Philippines are presented separately in Section "Case Review Results".

4.2.2. Case Review Results

4.2.2.1. Cases From the Philippines (n=325)

As detailed above, the 325 cases from the Philippines were reviewed separately from the remaining 353 cases. Most of these cases reported increased BP (n=311), 13 cases referred to hypertension, and 1 case to hypertensive heart disease. The number of cases was comparatively distributed across sex (178 females and 144 males; sex was not reported in 3 cases) and most of the cases involved adults (n=223).

Mean and median ages were 57.5 years and 58 years, respectively, and the age range was 19 to 98 years. No baseline BP values were provided in any of the cases, whereas the BP post-vaccination corresponded to Grade 3 in 303 cases, Grade 2 in 2 cases or was not reported in 20 cases.

The 325 cases reported 325 EOIs. None of the 325 cases provided information on duration of the EOI. In 307 of the 325 cases, the event was noted on the same day of vaccination, and in the majority of these cases, hypertension was resolved/resolving at the time of reporting (n=299). No information regarding clinical context, including the patients' medical histories/concurrent conditions, and/or concomitant medications was provided in the 307 cases, which precluded a meaningful medical assessment. Considering the short TTO , the reported events in the 307 cases could represent an unmasking of pre-existing hypertension and/or transient hypertension triggered by vaccination-related anxiety.

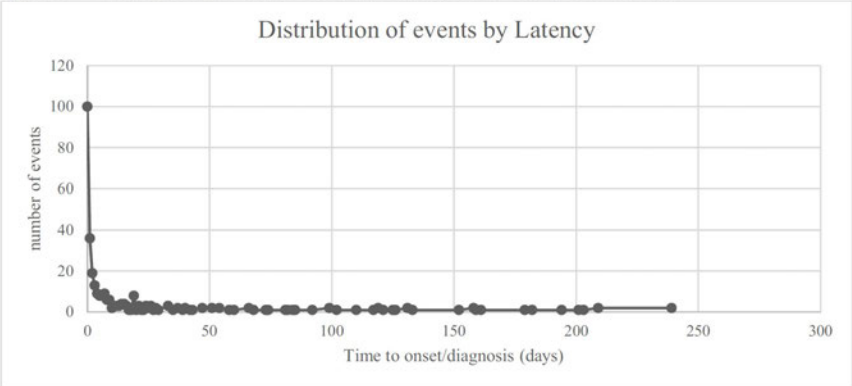
Time to onset/diagnosis of hypertension in 14 of the remaining 18 cases ranged from 2 to 30 days; whereas no information on latency was provided in 4 cases. The EOI occurred in the context of concurrent or past COVID-19 disease (n=3) or in patients whose medical history was not reported (n=15).

Fatal outcome was reported in 7 out of 325 cases. These 7 cases involved 4 females and 3 males. Median age of these 7 patients was 61 years (range 44 to 74 years). Median TTO of the EOI was 4 days (range 2 to 23 days). In 1 case the patient died in the context of critical COVID-19 pneumonia with hypoxia (n=1), whereas in the remaining 6 cases the reported cause of death was: cerebrovascular accident and hypertension (n=1), myocardial infarction and hypertension (n=1), hypertension, haematoma and malaise (n=1), hypertension or increased blood pressure (n=2) or fatigue, dysphagia, increased BP and chest pain (n=1). All 6 cases lacked information on the patient's medical history, concomitant medication, clinical information including diagnostic work up, treatment or autopsy results, precluding medical assessment. No safety concern was detected from the data in serious cases of hypertension from the Philippines, including those with fatal outcome.

Cases From the Remaining Regions (n=353)

Three hundred fifty-three cases were received from countries other than the Philippines. The most frequently reported events were hypertension (n=231 events), increased blood pressure (n=70 events), and hypertensive crisis (n=32 events); 152 cases were medically confirmed, and 201 cases were medically unconfirmed. One hundred ninety-four cases involved females, and 152 involved males; sex was not reported in 7 cases; and most of the cases involved adults (n=251). Mean and median ages were 53.8 years and 54 years, respectively and the age range was 18 to 95 years. Of the 368 EOIs reported in the 353 cases, 101 EOIs (28.3%) were noted on the same day of vaccination (Day 0), 36 EOIs on Day 1 and 19 EOIs on Day 2 after vaccination. Thus, a total of 42.3% of events were reported within first 2 days of vaccination (156/368). No information on TTO was provided for 47 out of the 367 events. Mean and median latency were 22.1 and 3 days, respectively. A distribution of cases by Time to onset/diagnosis is displayed in Figure 1 below.

Figure 1: Distribution of Events of Interest by Latency From Vaccine Administration



Baseline or historical BP values were only provided in a limited number of cases (n=22), whereas the BP noted post-vaccination corresponded to Grade 3 in 114 cases, Grade 2 in 32 cases, Grade 1 in 10 cases. No post-vaccination BP values were reported in 197 cases. Thirty-two cases involved patients with past or concurrent COVID-19 infection. Of the 368 EOIs, 43.5 % (160/368) were resolved or resolving at the time of reporting, 125 events (33.7%) were not resolved, and outcome for 70 events (19%) was not reported. Time to resolution was available for 49 of the 368 events, with 53.1% resolving on the same or next day (20 and 6 events, respectively). Duration of the remaining events ranged between 2 and 104 days. Mean and median duration for the 49 EOIs was 9.1 days and 1 day, respectively. In 15 of the 353 cases, the patient died. In 1 of the cases, hypertension resolved prior to death and in 2 cases, involving either multiple patients or an elderly patient who experienced diabetes and uncontrolled hypertension, the outcome of the EOI was not reported. In the remaining 12 cases, the EOI had a fatal outcome as follows:

- Median age of patients in these 12 fatal cases was 63.5 years (range 39 to 90 years). There were 5 females and 7 males amongst these 12 cases.
- In 4 of the 12 cases, the patients died due to manifestations of underlying conditions. The reported causes of death included haematemesis due to oesophageal varices (n=1, high BP was noted after patient was kept on "pressures" to maintain BP), hypertensive heart disease, obesity and chronic alcohol use (n=1), hypertension and diabetes (n=1, in a polymorbid patient with underlying primary hypertension, morbid obesity, hypercholesterolaemia and diabetes), and chronic heart failure, hypertension, coronary and aortic sclerosis (n=1, in a patient who was a heavy smoker)
- In 5 of the 12 cases, death occurred in the context of concurrent fatal events including COVID- 19 (n=2), aortic dissection and haemorrhagic stroke in a patient with underlying hypertension and use of tobacco (n=1) or thromboembolic events (n=2, myocardial infarction in 1 patient, and thrombosis in a patient who also experienced Fibrin D dimer increased, cardiac arrest, and renal failure), In these cases hypertension was likely a consequence of the concurrent coreported event.
- In 2 cases the cause of death was not reported however the course of the events was suggestive of a cause of death not related to vaccination. One case involved a patient who within 1 to 2 months post vaccination was diagnosed with- and treated for- an aggressive form of lymphoma; the patient passed away 1 week later, in the context of an Escherichia coli infection. One case referred to a 90-year-oldpatient who had lost his balance, had fallen within 4 days after vaccination and had laid on the floor for around 12 hours; the patient died in the hospital while being diagnosed with closed left hip fraction, bradycardia, coronary artery disease, hypokalemia, protein calorie malnutrition, type 2 myocardial infarction and essential hypertension.
- 1 case lacked information on the patient's medical history, concomitant medications or clinical context and referred to a 61-year-old female woman who experienced high BP (225/119) loss of

consciousness, being unresponsive, and died. The limited information in this case precludes any meaningful causality assessment.

No trend in the reported fatal events was observed, and in most of the cases the cause of death was related to the patients' concomitant condition or to medical history.

Overall, of the 353 cases, 14 cases included patients where hypertension was noted concurrent to anxiety, and 12 cases pertained to pregnant women. Concurrent thromboembolic, ischaemic or haemorrhagic events were described in 78 cases. Eighty-six cases contained limited information. All these and the remaining 163 cases are discussed in more detail by category below.

- Anxiety

Anxiety-related reactions are known to occur with all vaccinations including COVID-19 vaccination and are considered labelled events. Fourteen of the 353 cases reported hypertension in association with anxiety. The EOI included hypertension (n=10), increased BP (n=3) and hypertensive crisis (n=1).

In 7 of the 14 cases, hypertension was noted on the same day of vaccination, and potentially represented an immunisation anxiety-related reaction (n=6) or anxiety associated with symptoms of an allergic reaction, including tongue swelling and rash (n=1). In 3 of the 7 cases, the patients had underlying hypertension and 1 had a medical history of thyroidectomy (Eszter, 2019). In the remaining 7 cases, hypertension was noted from 1 to 26 days after vaccination (n=5) or TTO was not provided (n=2). The event occurred concurrent to anxiety and other events including: renal infarct (n=1); gastrointestinal issues and dyspnoea (n=1); vertigo, tachycardia, dry mouth, paraesthesia, muscular weakness, (n=1); tiredness, hypoaesthesia, unspecified blood clots, dyspnoea and chest pain (n=1); lymphadenopathy and muscular weakness (n=1), "a probable framework" of myocarditis (n=1); and cold sweat, gait disturbance, paraesthesia, hot flush, hyperhidrosis, chills and malaise (n=1). Three of the cases documented risk factors for high BP including underlying hypertension, use of oral contraceptives or alcohol (Husain 2014; Pimenta 2012). Altogether, hypertension could be due to anxiety triggered by the other events that followed vaccination in these cases.

None of the 14 cases had a fatal outcome

- Pregnancy

Twelve of the 325 cases involved pregnant women who experienced 1 or more of the following events: preeclampsia (n=8), BP increased (1), gestational hypertension (n=2), hemolysis elevated liver enzymes, low platelet count (HELPP) syndrome (n=2), or eclampsia (n=2). Most ofthe cases were from the C-VIPER pregnancy registry (10/12). The median age range was 26 to 36 years with mean and median ages of 32.8 and 33 years, respectively. Four women received Ad26.COV2.S during the first trimester of pregnancy, 4 women were vaccinated during the second trimester, and 4 during the third trimester. In all cases, the EOI occurred during the third trimester of pregnancy, irrespective of timing of vaccination. Latency of the EOIs ranged between 2- and 203-days post-vaccination (mean 85.1 and median 99 days). Four cases documented risk factors for the events including: history of preeclampsia, overweight, and diabetes mellitus (Bryson, 2003; Spiegler, 2013; Umesawa, 2017) and 3 of the 7 women had a history of spontaneous abortions/miscarriages. In addition, past or concurrent COVID-19 was reported in 3 cases. No fatal outcomes (maternal or fetal) were reported in cases involving pregnant women. Pregnancy outcome was live birth in all cases, with 1 birth premature at gestational age 36 weeks 2 days.

In view of the maternal underlying conditions, past medical history or the obstetrical history and the absence of pattern in latency, the causal role of the Ad26.COV2.S vaccine to the events of hypertension seen in pregnant women is unlikely.

- Thromboembolic, haemorrhagic or ischaemic events

Seventy-eight cases reported the event of hypertension in patients who experienced thromboembolic, haemorrhagic, and/or ischaemic events. The median age range in these cases was 33 to 90 years with mean and median ages respectively of 59.7 and 59 years.

These 78 cases reported a total of 84 EOIs, with the most frequently reported events being hypertension (n=58) and BP increased (n=16). Latency of the 84 EOIs ranged between same day and 239 days post-vaccination (Mean: 38.3 days and Median: 15 days). Twenty-six EOIs (30.9%, 26/84) were resolved or resolving at the time of reporting, 36 events (42.8%) were not resolved, 5 (6.0%) had a fatal outcome and the outcome for 17 events (20.2%) was not reported.

The 5 fatal events reported in 5 cases are included in the total of 12 cases described above. These cases involved 3 males and 2 females. Median age (calculated from the 3 cases with age reported), was 77 years. Median TTO of the fatal events was 4 days (range 2 to 23 days). Death occurred in the context of concurrent COVID-19 (n=2), haemorrhagic stroke (n=1) or thromboembolic events (n=2).

Time to resolution of hypertension was available for 1 of the 84 EOIs and was 1 day. None of the cases provided baseline or historical BP values. Hypertension is well established to be associated with thromboembolism with or without thrombocytopenia which may represent an alternative aetiology, as thromboembolic events can elicit a hypertensive response post-stroke (Qureshi, 2008; Qureshi 2018). Hypertension is also a risk factor for thromboembolic, haemorrhagic, and/or ischaemic events. In this context, it is important to note that most of the cases were reported in patients with significant risk factors for hypertension and thromboembolic events. Ofthe 78 cases, 75.6% (59/78) referred to patients with confounding underlying conditions. This included 35 cases (44.9%, 35/78) that reported preexisting hypertension, and 16.7% (13/78) that involved patients with concurrent or past COVID-19 infection. A detailed breakdown of the cases by reported thromboembolic, haemorrhagic or ischaemic event as well as other risk factors/alternative aetiologies is presented below in Table 3.

Table 6: Studies Reporting Serious Hypertension After COVID-19 Vaccine Administration

Author	Study Type Details	Patient Details	Study Results	Other Relevant Information	MAH comment
mRNA and Adenovirus Vector Vaccines					
Bouhanick[a]	Retrospective Data mining review of VigiBase® - reports with known age (≥18 years) and sex reported with Pfizer (tozinameran), AZ (Vaxzevria), Moderna (mRNA-1273), or NRVV-Ad26 Janssen vaccines between 1 January 2021 and 10 May 2021 Cases containing the MedDRA PT Hypertension and defined as "suspected or interacting" and non-cases all other reports Sensitivity analyses were performed, first, including only hypertension	N=175,916 reports/COVID-19 vaccinated n=91,761 • 1,776 hypertension including: ○ 1,325 tozinameran (mean age 62 [18] years, 76% females, 5% antihypertensives, 1% antidiabetics) ○ 392 Vaxzevria (59.1 [13.9] years, 64% females, 7% antihypertensives, 1% antidiabetics) ○ 58 mRNA-1273 (71.9 [15.9] years, 88% females, 10% antihypertensives, 3% antidiabetics) ○ 1 NRVV-Ad26	• Tozinameran was associated with a higher risk of hypertension compared to nonusers (ROR=2.25 [2.08 to 2.43]) • No association was found for Vaxzevria (ROR=1.02 [0.92 to 1.14] or mRNA-1273 (ROR=0.88 [0.68 to 1.14]) • A higher reporting risk was also found for tozinameran versus Vaxzevria or mRNA-1273 in the whole population as well as in the different age groups. An increase in RORs including only hypertension occurring 24 hr, 48 hr and 72 hr after vaccination was observed (39% occurred after 24 hr, 26% after 48 hr, and 20% after 72 hr)	The authors proposed an increase in sympathetic tone for immediate hypertension and/or an interaction with the renin-angiotensin system for tardive hypertension. In addition, involvement of vaccine excipients was also suggested. However, the majority of cases with tozinameran found hypertension was delayed. The authors identified limitations to the study including underreporting, based on spontaneous reporting, and the possibility of confounding, such as comorbidities and/or unknown data.	This paper published as a letter to the editor should not be used to assess a causal relationship or an association between Ad26.COV2.S and serious hypertension. Notably, the data from VigiBase®do not include a comparison of the risk for the EOI with COVID vaccines to the risk of the EOI in the remainder of the VigiBase® reports. The study data include only 1 report of hypertension with Ad26.COV2.S. No relative association with the EOI was presented for Ad26.COV2.S.

Author	Study Type Details	Patient Details	Study Results	Other Relevant Information	MAH comment
	occurring after 24 hr, 48 hr, or 72 hr in order to investigate occurrence delays and second, according to age groups (18 to 44, 45 to 64, 65 to 74, and ≥75 years). Risk was calculated using ROR.				
Sanidas[b]	Prospective study of 100 subjects between the age of 50 years to 70 years randomly assigned to the Pfizer, AZ, Moderna, or J&J vaccine. Half were hypertensives under medical treatment and half were not. All subjects had SBP <140 mmHg and DBP <90 mmHg prior to vaccination.	• Hypertensives (n=50): 64±7.2 years; 25 males, 25 females; BMI (kg/m^2) 28.3±4.5 • Healthy controls (n=50): 58±8.2 years; 25 males, 25 females, BMI (kg/m^2) 27.8±1.5 p values: Age (years) 0.007; male gender 0.1	• Hypertensives: home BP mean – SBP 174.7±39.8, DBP 97.3±5.8; 24-hour BP mean – SBP 176.7±42.4, DBP 98.3±8.1 • Healthy controls: home BP mean – SBP 157.6±44.1, DBP 95.8±7.3; 24-hour BP mean – SBP 155.6±35.9, DBP 93.8±5.7 p values: BMI 0.02; home BP mean SBP 0.001, DBP 0.05; 24-hour BP mean SBP 0.001, DBP 0.06 Five of 50 hypertensive subjects received additional medication whereas some of the non-hypertensive patients started life-style modification changes	The authors acknowledged that the pathophysiological link between COVID-19 vaccines and an increase in BP remains unclear. However, regarding mRNA vaccines, it has been noted that mRNA encodes the Spike protein of SARS-CoV-2 in the cells reached by the vaccines. In turn, the Spike proteins congregate into the cytoplasm and migrate to cell surfaces to protrude with a native-like confirmation to be recognised by the immune system. Moreover, Spike proteins circulate in blood as free-floating proteins after cells being destroyed and	This paper published as a letter to the editor should not be used to assess a causal relationship or an association between Ad26.COV2.S and serious hypertension. Notably, the data do not include a comparison of the risk for the EOI with COVID vaccines to the risk of the EOI in a comparator group. The study data include an unknown number of reports with Ad26.COV2.S. No relative association with the EOI was presented for Ad26.COV2.S.

Author	Study Type Details	Patient Details	Study Results	Other Relevant Information	MAH comment
	Standard daily home BP measurements were recorded as well as ABPM between Day 5 and Day 20 post vaccination.		and systematic BP measurements for a possible diagnosis of hypertension	interact with ACE2 receptors resulting in the internalisation and degradation of the receptors. The loss of ACE2 receptor activity and the inactivation of angiotensin II decrease the production of angiotensin 1-7. The subsequent imbalance between angiotensin II (overactivity) and angiotensin 1-7 (deficiency) was proposed to play a role in the pathogenesis of hypertension after COVID-19 vaccination. Alternative explanations include response to excipients, emotional/stress/pain responses, white coat syndrome, and undiagnosed hypertension. (see section biological plausibility).	
mRNA Vaccines					
Zappa[c]	Prospective Questionnaire study – 70 questions focusing on comorbidities and type of ADR including rise in BP (defined by an average rise in home SBP or	• N=113 ○ Females 73%; current smokers 15%; mean age 43±11 years. Prevalence of hypertension 18%, diabetes mellitus 1% dyslipidaemia 19%, and asthma 10%. A previous	• 6 subjects (5.3%) showed a mean rise in SBP or DBP at home by ≥10 mmHg during the first 5 days post vaccination when compared with the 5 days prior to vaccination ○ 4 females, 2 males; Age range 35 years to 52 years	NA	This paper published as a letter to the editor should not be used to assess a causal relationship or an association between Ad26.COV2.S and serious hypertension. Notably, the data do not include a comparison of the risk for the EOI with COVID vaccines to the risk in a comparator group. The study data do not include

Author	Study Type Details	Patient Details	Study Results	Other Relevant Information	MAH comment
	DBP by at least 10 mmHg from the 5 days prior or the 5 days post vaccination). Subjects received 2 doses of the Pfizer BioNTech vaccine	myocardial infarction was recorded in 1 subject and 13 subjects had a previous documented exposure to SARS-CoV-2	○ BP lowering drugs reported in 5 of 6 subjects, including calcium-channel blockers (n=2), beta-blockers (n=3), ACE inhibitors (n=2), and diuretic (n=1) ○ Comorbidities were identified in 4 subjects and included dyslipidaemia (n=2), diabetes mellitus (n=1), and ischaemic heart disease (n=1) ○ BMI ranged from 20.4 to 27.6 kg/m^2. • Home BPs prior to vaccination for these subjects: 100/60, 125/70, 115/70, 120/65, 125/75, and 135/65 • Home BP after vaccination (first dose): 115/75, 144/92, 154/102, 130/85, 195/105, 185/115 • Increase in BP required intensification of BP-lowering treatment in 4 subjects		reports of hypertension with Ad26.COV2.S. No relative association with the EOI was presented for Ad26.COV2.S.

Author	Study Type Details	Patient Details	Study Results	Other Relevant Information	MAH comment
			• 2 subjects who experienced an increase in BP after the first dose also experienced it after the second dose (120/78, 150/94) • History of COVID-19 infection was associated with a higher incidence of rise in BP when compared with subjects without previous exposure (23% versus 3%, p=0.002) • Other ADRs also reported in 5 of the 6 subjects and included fever, headache, myalgia, diarrhoea, and loss of taste/smell		

Key: ABPM=Ambulatory Blood Pressure; ACE=Angiotensin-converting Enzyme; ADR=Adverse Drug Reaction; AZ=AstraZeneca; BMI=Body Mass Index; BP=Blood Pressure; COVID-19=Coronavirus Disease-2019; DBP=Diastolic Blood Pressure; J&J=Johnson & Johnson; MedDRA=Medical Dictionary for Regulatory Activities; MOA=Mechanism of Action; mRNA=Messenger Ribonucleic Acid; NA=Not Applicable; PT=Preferred Term; ROR=Reporting Odds Ratio; SARS-CoV-2=Severe Acute Respiratory Syndrome Coronavirus 2; SBP=Systolic Blood Pressure.

a: Bouhanick B, Montastruc F, Tessier S, et al. Hypertension and Covid-19 vaccines: are there any differences between the different vaccines? A safety signal. *Eur J Clin Pharmacol.* 2021;77(12):1937-1938.

b: Sanidas E, Anastasiou T, Papadopoulos D, Velliou M, Mantzourani M. Short term blood pressure alterations in recently COVID-19 vaccinated patients. *Eur J Intern Med.* 2021;29:29. doi.org/10.1016/j.ejim.2021.11.017. One case in this paper referred to J&J vaccine and was received post DLP of this report. Hence it is not included in the aggregate assessment of cases presented above.

c: Zappa M, Verdecchia P, Spanevello A, Visca D, Angeli F. Blood pressure increase after Pfizer/BioNTech SARS-CoV-2 vaccine. *Eur J Int Med.*2021;90:111-113.

Table 3: Risk Factors/Alternate Aetiology for Cases Reporting Hypertension and Thromboembolic, Haemorrhagic or Ischaemic events With the Use of Ad26.COV2.S (n=78)

Confounding Concurrent Condition/Medical History/Concomitant Medication	Number of Cases[a]
Thromboembolic, haemorrhagic or ischaemic events	
Cerebrovascular accident	18
Thrombosis	15
Pulmonary embolism	13
Transient ischaemic attack	8
Acute myocardial infarction	5
Myocardial infarction	5
Cerebral haemorrhage	3
Cerebral infarction	4
Ischaemic stroke	3
Other Thromboembolic, haemorrhagic or ischaemic events[b]	25
Other underlying risk factors/alternative aetiologies	
Underlying hypertension	35
Obesity/Dyslipidaemia/cholesterolaemia[c]	14
Diabetes[d]	13
Past or concurrent COVID-19[e]	13
Thyroid disease[f]	8
Underlying heart disease including Coronary artery disease, Ischaemic heart disease, History of triple bypass open heart surgery[g]	4
Chronic kidney disease[h]	4
Concurrent strong pain in context of sickle cell crisis or migraine[i]	3
Autoimmune disease (Systemic Lupus Erythematosis, psoriasis)[j]	2
Other[k]	9

Key: n= Number; COVID-19=Coronavirus Disease-2019

a: A single case was confounded by more than 1 medical history/concurrent condition

b: This includes n=2 cases each for cerebral artery thrombosis, cerebral thrombosis, cerebral venous sinus thrombosis, embolic stroke, pulmonary thrombosis; venous thrombosis; and 1 case each for basal ganglia stroke, brain stem stroke, carotid artery thrombosis, cerebral artery embolism, cerebral venous thrombosis, haemorrhagic stroke, ischaemic cerebral infarction, lacunar stroke, thalamic infarction, jugular vein thrombosis, superficial vein thrombosis, haemorrhagic stroke, ophthalmic artery thrombosis, thrombosis with thrombocytopenia syndrome.

c: Jiang, 2016; Obesity and hypertension. Chongthawonsatid, 2015 ; Relationship between Dyslipidemia and Hypertension.

d: De Boer, 2017; Diabetes and Hypertension: A Position Statement by the American Diabetes Association Diabetes Care.

e: Chen, 2021; Hypertension as a sequela in patients of SARS-CoV-2 infection.

f: Eszter, 2019; Hypertension in Thyroid Disorders

g: Dzau, 2019; Atherosclerosis and hypertension: mechanisms and interrelationships. Dzeshka, 2017 Atrial fibrillation and hypertension. Chiong, 2008; Secondary hypertension: current diagnosis and treatment.

h: Tedla, 2011; Hypertension in chronic kidney disease: navigating the evidence.

i: Sacco, 2013; The Relationship Between Blood Pressure and Pain.

j: Wolf, 2019; Autoimmune Disease-Associated Hypertension.

k: this included n=2 cases each for Chronic Obstructive Pulmonary Disease (Imaizumi 2021; Lung Disease and Hypertension); underlying anxiety or stress (Johnson, 2019; Anxiety and Hypertension: Is There a Link?) and n=1 case each for oral contraceptives (Pimenta, 2012; Hypertension in woman); adrenal mass (Moneva, 2002; Pathophysiology of adrenal hypertension); elevated BP during Bruce protocol; methylenetetrahydrofolate reductase deficiency (Garfunkel, 2003; Hyperhomocysteinemia but not MTHFR genotype is associated with young-onset essential hypertension) and polycythemia (Onusko, 2003; Diagnosing secondary hypertension)

- Other cases

Of the remaining 249 cases, 86 cases lacked information on the patient's medical history, concomitant medication and/or clinical details including latency and/or diagnostic work-up data, which precluded a meaningful medical assessment. EOIs in these 86 cases were hypertension (n=57), hypertensive crisis and hypertensive urgency (n=16), and increased BP (n=14). These cases are not discussed further.

The age range in the remaining 163 cases was 18 to 95 years, with mean and median ages of 55.7 and 56 years, respectively.

These 163 cases reported a total of 168 EOIs, with the most frequently reported events being hypertension (n=106) and blood pressure increased (n=36). Latency of the 168 EOIs ranged between same day and 209 days post-vaccination (mean 17.6 days and median 2 days). Fifty-six of the EOIs occurred on the day of vaccination.

Seventy-seven EOIs (45.8%, 77/168) were resolved, or resolving at the time of reporting, 55 events (32.7%) were not resolved, 6 (3.6%) had a fatal outcome, and the outcome for 30 events (17.8%) was not reported.

The 6 fatal events reported in 6 cases are included in the total of 12 cases described above. The 6 cases involved 4 males and 2 females. Median age of patients was 58.5 years. Median TTO was 2.5 days (range 1 to 102). Death occurred in association with concurrent events including COVID 19, lymphoma and infection, or in the context of underlying disease (4 cases as described above who died due to manifestations of underlying conditions).

Time to resolution of hypertension was available for 29 of the of the 168 events (range Day 0 to Day 73; with a mean duration of 5.8 days, and a median duration of 1 day). Nineteen of the cases reported historical or pre-vaccination BP values.

Most of the cases (88.3%, 144/163) documented at least 1 risk factor or a condition presenting a possible alternative aetiology which may have contributed to the EOI. Most frequently reported underlying conditions in these 144 cases were pre-existing hypertension (59%, 85/144), obesity/dyslipidaemia (20.1%, 29/144), thyroid disease (12.5%, 18/144) and concurrent or past COVID-19 infection (11%, 16/144). A detailed breakdown of the cases is presented below in Table 4.

Table 4: Risk Factors/Alternate Aetiology for Cases Reporting Hypertension With the Use of Ad26.COV2.S (n=163)

Confounding Concurrent Condition/Medical History/Concomitant Medication[a]	Number of Cases[a]
Underlying Hypertension	85
Obesity/Dyslipidaemia[b]	29
Thyroid disease[c]	18
Past or concurrent COVID-19[d]	16
Diabetes[e]	13
Concomitant or medical history of anxiety disorder/stress/panic attacks/depression[f]	11

Table 4: Risk Factors/Alternate Aetiology for Cases Reporting Hypertension With the Use of Ad26.COV2.S (n=163)

Confounding Concurrent Condition/Medical History/Concomitant Medication[a]	Number of Cases[a]
Concurrent strong pain[g]	6
Kidney disease[h]	5
Confounding medication for treatment of underlying or concurrent conditions (tacrolimus, cortisone, corticosteroids, epinephrine, or unspecified intervention to maintain blood pressure in patient who experienced haematemesis treated by oesopageal varices ligation)[i]	8
Smoking/nicotine dependence[j]	6
COPD[k]	5
Guillain Barré syndrome[l]	5
Gastro-oesophageal reflux disease[m]	2
Oral ontraceptives[n]	2
Other[o]	7

Key: n= Number; COVID-19=Coronavirus Disease-2019, COPD=Chronic Obstructive Pulmonary Disease.

a: A single case maybe confounded by more than 1 medical history/concurrent condition.
b: Jiang, 2016; Obesity and hypertension. Chongthawonsatid, 2015 ; Relationship between Dyslipidemia and Hypertension.
c: Eszter, 2019; Hypertension in Thyroid Disorders
d: Chen, 2021; Hypertension as a sequela in patients of SARS-CoV-2 infection.
e: De Boer, 2017; Diabetes and Hypertension: A Position Statement by the American Diabetes Association Diabetes Care.
f: Johnson, 2019; Anxiety and Hypertension: Is There a Link?
g: Sacco, 2013; The Relationship Between Blood Pressure and Pain.
h: Tedla, 2011; Hypertension in chronic kidney disease: navigating the evidence.
i: Tacrolimus SmPC, Epinephrine SmPC,
j: Unger 2020; 2020 International Society of Hypertension Global Hypertension Practice Guidelines.
k: Imaizumi 2021; Lung Disease and Hypertension
l: Singh, 2020; Frequency of Autonomic Dysfunction in Patients of Guillain Barre Syndrome in a Tertiary Care Hospital
m: Li, 2018; The Role of Gastroesophageal Reflux in Provoking High Blood Pressure Episodes in Patients With Hypertension.
n: Pimenta, 2012; Hypertension in woman
o: 1 case each of: renal cell carcinoma (Stojanovic, 2009; Renal cell carcinoma and arterial hypertension); renal cyst (Kim, 2014; Relationship of Simple Renal Cyst to Hypertension); neuroendocrine tumor (Santos, 2019; Diagnosis and treatment of neuroendocrine tumors – A series of 13 clinical cases); Cushing's syndrome (Unger, 2020; 2020 International Society of Hypertension Global Hypertension Practice Guidelines); vasculitis (Zhu, 2019; Systemic vasculitis: an important and underestimated cause of malignant hypertension); CAD (coronary bypass 4 days after vaccination, indicating pre-existing CAD- Chiong, 2008; Secondary hypertension: current diagnosis and treatment); and underlying blood pressure fluctuation.

In 8 of the 19 remaining cases, hypertension was noted after vaccination in patients who experienced an immediate allergic reaction (n=4) anaphylaxis (n=1), manifestations of reactogenicity (n=1) or other symptoms which possibly represented anxiety-related reactions including palpitations, shortness of breath and tremor (n=1) or atypical chest pain (no abnormal test results, n=1).

In a further 3 cases, the EOI was an incidental finding in patients who presented at the Emergency Room (ER) either due to loss of consciousness and trauma, lymphatic mass in armpit (ball size), or after vaccine overdose, and in 1 case the event was incidentally noted during a visit to the dentist's office on the same day of vaccination.

One case reported hypertension in a patient with a flare of ulcerative colitis (no information on treatment provided) and in 1 case, the patient had normal BP values at Day 43 post-vaccination and was diagnosed with hypertensive crisis and diverticulitis 20 days later.

In 1 case, based on the latency of 209 days, a causal association of the event of hypertension with vaccination was considered unlikely.

In 2 cases, there was no clear explanation for the event of hypertension; in 1 case the event (elevated BP

1 hour post vaccination) was treated with lisinopril and diuretics (hydrochlorothiazide); and in the second case the event (hypertensive heart disease) was noted in a 46-year-old male patient, approximately 1 month after vaccination. Although in these 2 cases hypertension could have been pre-existing, a causal association of the events with use of Ad26.COV2.S cannot be excluded.

In 1 of the 2 remaining cases, hypertension occurred in a 76-year-old patient who also experienced upper motor neuron lesion, hemiparesis, facial paresis and haematuria, 2 months after vaccination. The concomitant upper motor neuron lesion and the long TTO in this case could indicate a cause other than vaccination for hypertension. The second case referred to a 43-year-old patient who experienced a sublingual haematoma (with normal platelet counts), 1 day after vaccination and proteinuria/hematuria (TTO not provided). In this case a contribution of the vaccine could not be excluded considering that sublingual hematoma could be secondary to severe hypertension (Satpathy 2015) or could be secondary to thrombocytopenia and coagulation disorders including heparin induced thrombocytopenia. In view of the patient's age however, (43 years), undetected pre-existing hypertension could not be ruled out. The patient had no other symptoms besides myalgia.

None of the 19 cases provided baseline or historical BP values.

PRAC Rapporteur comment:

In the global safety database 678 cases of severe hypertension were detected, covering 656 cases from spontaneous reports.

Of note, almost half of the cases stem from one country, i.e. the Philippines were BP measurement is part of the routines in the frame of the vaccination program. Of note, cases were reported as increased BP (n=311), 13 cases referred to hypertension, and 1 case to hypertensive heart disease. 7 cases were fatal. Many of these cases had no information regarding blood pressure before vaccination and were lacking other information regarding medical history, showed a very short TTO with start on the same day of vaccination and resolved later on.

The other 353 cases stem from other parts of the world. The most frequently reported events were hypertension (n=231 events), increased blood pressure (n=70 events), and hypertensive crisis (n=32 events). BP noted post-vaccination corresponded to Grade 3 in 114 cases, Grade 2 in 32 cases, Grade 1 in 10 cases. About 40% of the cases occurred within 2 days after vaccination. 12 events were fatal with either insufficient information regarding medical history or concurrent underlying diagnoses as confounders which might have caused the event. Events occurred in 14 cases together with anxiety (short TTOs), in 12 cases together with pregnancy (3rd trimester) and in 78 cases together with thromboembolic events. Remaining cases lacked either information regarding medical history or were confounded by other risk factors.

Literature

Review of the literature revealed 5 citations deemed relevant to the research question. Details are provided below.

The search of the literature identified 2 case reports/series involving hypertension and COVID-19 vaccines with both citing the administration of mRNA vaccines in patients who developed serious hypertension within 3 days post vaccination.

The first publication (Athyros 2021) concerned a 71-year-old female who experienced a fatal right intracranial haemorrhage 3 days after the administration of the first dose of the Moderna vaccine. Baseline blood pressure was 110/70 mmHg; however, medical history and concurrent conditions were not reported. The second (Meylan 2021) involved a case series of 9 patients from a large vaccination center

in Switzerland. The median age was 73 years with 8 of 9 patients having a history of well controlled pre-existing hypertension. Eight patients received the Pfizer/BioNTech vaccine and 1 the Moderna vaccine. On the same day as vaccination, all experienced Grade 2 (n=1) or Grade 3 (n=8) hypertension with 7 of 9 requiring medical intervention. All patients recovered. Specific details regarding these case reports are provided below in Table 5.

Table 5: Literature Case Reports/Series of Serious Hypertension After COVID-19 Vaccine Administration

Author	Age (Years)/Sex	Vaccine/Dose #	Risk factors/Alternate Aetiologies	Latency From Most Recent Dose	Baseline BP (mmHg) Elevated BP Levels (mmHg) Hypertension (Grade)	Summary of Other Presenting Symptoms/Laboratory Tests/Diagnostics/Treatments Outcome	Other Relevant Information
Athyros[a]	71/Female	Moderna/Dose #1	No previous medication or bleeding tendency noted	3 days	110/70 (prior to vaccination) 210/110 (Grade 3)	Right hemiplaegia, aphasia, and agnosia. CT showed an intracranial haemorrhage in the left basal ganglia. The patient was treated with 4 IV doses of 0.15 mg clonidine hydrochloride and 2 IV doses of furosemide (20 mg). However, her BP remained elevated (>180/100 mmHg), despite treatment. There was no thrombocytopenia or other abnormal blood tests noted. Nine days after the initial event, the patient died. Fatal	NA
Meylan[b]	Lausanne Switzerland vaccination centre with 13,296 vaccine doses administered (12,349 first doses, 947 second doses). All AEs were reported to Swissmedic. Case series – 9 patients: median age 73 (IQR 22) years; 7females/2 males	BNT162b2 (n=8), mRNA-1273 (n=1)/All received Dose #1	• 8/9 history of arterial hypertension with most receiving treatment with antihypertensive therapy. All reported well controlled hypertension • 1 patient had a history of cerebral aneurysm that was coiled within the past year with a targeted SBP <140 mmHg. Due to developing headache, the patient underwent imaging with no sign of intracranial haemorrhage	Same day	NR 170/111 (Grade 3), 181/90 (Grade 3), 182/101 (Grade 3), 177/88 (Grade 2), 168/115 (Grade 3), 200/100 (Grade 3), 180/106 (Grade 3), 183/98 (Grade 3), 220/102 (Grade 3)	• Symptoms ranged from malaise, headache, chest pain, diaphoresis, anxiety, tingling in mouth, and swelling at injection site. • HR ranged from 65 bpm to 88 bpm • Treatment varied from transfer to the ER to administration of antihypertensives • 1 case spontaneously resolved and 1 patient refused monitoring and work-up All patients recovered	The authors speculated on potential MOAs including a stress or pain response. In addition, the white coat effect was considered, typically being associated with age and female sex. However, due to the relatively low HRs observed, this was deemed unlikely. Alternative theories included hypertension due to adjuvants, such as PEG although this seemed unlikely due to the presumably low dosage and as patients reacted within minutes of the injection. As tromethamine is only contained in the mRNA-1273 vaccine, its causative role was ruled out. An interaction between the S-protein and angiotensin converting enzyme 2 also seemed highly unlikely as patients reacted within minutes not leaving time for mRNA cellular uptake, translation, and S-protein presentation at the membrane of macrophages and dendritic cells.

Key: AE=Adverse Event; BP=Blood Pressure; CT=Computed Tomography; ER=Emergency Room; HR=Heart Rate; MOA=Mechanism of Action; mRNA=Messenger Ribonucleic Acid; NA=Not Applicable; NR=Not Reported; IQR=Interquartile Range; IV=Intravenous; PEG=Polyethylene Glycol; SBP=Systolic Blood Pressure.

a: Athyros VG, Doumas M. A possible case of hypertensive crisis with intracranial haemorrhage after an mRNA anti-COVID-19 vaccine. *Angiology.* 2022;73(1):87.

Table 5: Literature Case Reports/Series of Serious Hypertension After COVID-19 Vaccine Administration

Author	Age (Years)/Sex	Vaccine/Dose #	Risk factors/Alternate Aetiologies	Latency From Most Recent Dose	Baseline BP (mmHg) Elevated BP Levels (mmHg) Hypertension (Grade)	Summary of Other Presenting Symptoms/Laboratory Tests/Diagnostics/Treatments Outcome	Other Relevant Information

b: Meylan S, Livio F, Foerster M, et al. Stage III hypertension in patients after mRNA-based SARS-CoV-2 vaccination. *Hypertension.* 2021;77(6):e56-e57.

The search of the literature also identified 3 studies (2 prospective, 1 retrospective) involving serious hypertension and COVID-19 vaccines. Two of the studies concerned the use of mRNA and adenovirus

vector vaccines and the third solely mRNA vaccine administration. Bouhanick 2021 performed data mining in the World Health Organisation (WHO) Vigibase® for reports of hypertension with use of the Pfizer, Moderna, AstraZeneca, and Janssen vaccines. The authors identified a higher reporting risk in all populations, including when stratified by age group, for the Pfizer BioNTech vaccine versus the Moderna or AstraZeneca vaccines. Furthermore, an increase in the reporting odds ratios (ROR) at 24 hours, 48 hours, and 72 hours post vaccination was also observed. In a prospective cohort study, Sanidas 2021 compared 50 hypertensives versus 50 healthy controls who had received either an adenovirus vector or mRNA COVID-19 vaccine. The authors found that all subjects, regardless of hypertensive history, recorded a hypertensive response defined as a SBP value ⩾140 mmHg and/or DBP value ⩾90 mmHg between Day 5 and Day 20 post vaccination, irrespective of vaccine type. Hypertensives were older and with a higher BMI. Lastly, Zappa 2021 performed a prospective study focusing on comorbidities and post vaccination events, including increases in blood pressure. Of the 113 subjects enrolled, 5.3% (n=6) showed a mean rise in SBP or DBP at home by ⩾10 mmHg during the first 5 days post vaccination when compared to the 5 days prior to vaccination. Five of these subjects had a pre-existing history of hypertension. Furthermore, a history of COVID-19 infection was associated with a higher incidence of rise in BP when compared with subjects without previous exposure (p=0.002). Specific details regarding these studies are provided below in Table 6. In addition, a summary of pathogenesis and suggested MOAs are presented in Section Biological Plausibility. Of note, the 3 studies, presented as letters to the Editor, do not provide meaningful evidence supporting a causal relationship or an association between Ad26.COV2.S and serious hypertension. The presented analyses only included events after vaccination without inclusion of a comparison group (unvaccinated population). No relative association with the EOI (serious hypertension) was presented for Ad26.COV2.S in any of the 3 studies.

PRAC rapporteur comment:

Literature study did not identify a clearly described association between the Janssen Covid-19 vaccien and hypertension.

Observed Versus Expected Analysis

A cumulative broad O/E analysis with sensitivity analysis was performed for regions: EU and US. The following age-group stratifications were used per sex: 18 to 29, 30 to 39, 40 to 49, 50 to 64, 65 to 74, ⩾ 75 years). Observed counts included cases with events of interest that occurred within the risk window (Day 1-42), and cases where time-to-onset (TTO) was 0 or not reported. Background incident rates for hypertension stratified by severity or grade were not available following a review of the Epidemiological literature. Therefore, background incidence rates from the ACCESS report (FISABIO, 2018 – ACCESS report June 2021) were used without any distinction in severity level. The O/E analysis was performed including all post-marketing cases of hypertension within the GMS global safety database (irrespective of severity or grade). The following search strategy for All hypertension included: Hypertension (SMQ Narrow). A conservative risk window of Day 1-42 was used, with consideration made to hypertension latency distribution. See Section 3.4, for O/E calculation method.

Results of the EU and US broad analysis to include sensitivity analysis are presented in Table 7 and Table 8 respectively below.

Table 7: EU Broad O/E and Sensitivity Analysis Results- All Hypertension

Broad O/E Analysis						Sensitivity Analysis	
Sex	Age Range (Years)	Exposure[a] (100,000 PY)	Observed Count[b]	O/E Ratio (95% CI)[c,d] (PE, 100% RP)		O/E Ratio (95% CI)[c,d] (LB, 50% RP)	
Male	18 – 29	2.043	13.33	0.039	(0.021, 0.067)	0.086	(0.046, 0.146)
	30 - 39	1.818	23.24	0.020	(0.012, 0.029)	0.041	(0.026, 0.061)
	40 – 49	1.809	27.66	0.008	(0.005, 0.011)	0.016	(0.011, 0.023)
	50 – 64	2.712	53.19	0.004	(0.003, 0.005)	0.008	(0.006, 0.011)
	65 – 74	0.889	13.90	0.002	(0.001, 0.004)	0.004	(0.002, 0.007)
	≥75	0.355	3.99	0.001	(0.000, 0.003)	0.002	(0.001, 0.006)
Female	18 – 29	1.938	8.53	0.026	(0.011, 0.049)	0.056	(0.025, 0.108)
	30 - 39	1.790	21.13	0.019	(0.012, 0.030)	0.041	(0.025, 0.062)
	40 – 49	1.799	27.44	0.011	(0.007, 0.016)	0.022	(0.015, 0.032)
	50 – 64	2.821	61.61	0.006	(0.005, 0.008)	0.012	(0.010, 0.016)
	65 – 74	1.030	25.38	0.004	(0.003, 0.006)	0.008	(0.005, 0.012)
	≥75	0.552	7.30	0.001	(0.001, 0.003)	0.003	(0.001, 0.006)

Key: CI=Confidence Interval; EU=European Union; LB=Lower Bound; O/E=Observed versus Expected; PE=Point Estimate; PY=Person Years; RP=Reporting Percentage.

a: Exposure in the EU- DLP 30 November 2021. Source: ECDC (2021) for EEA, Vaccine Tracker - https://qap.ecdc.europa.eu/public/extensions/COVID-19/vaccine-tracker.html#distribution-tab

b: Counts included cases with events of interest that occurred within the risk window (1-42 days), and cases where time-to-onset was 0 or not reported.

c: Background Incidence Rate source: ACCESS (data FISABIO, 2018 – ACCESS report June 2021).

d: Poisson exact confidence interval (95% CI).

Table 8: US Broad O/E and Sensitivity Analysis Results- All Hypertension

Broad O/E Analysis						Sensitivity Analysis	
Sex	Age Range (Years)	Exposure[a] (100,000 PY)	Observed Count[b]	O/E Ratio (95% CI)[c,d] (PE, 100% RP)		O/E Ratio (95% CI)[c,d] (LB, 50% RP)	
Male	18 – 29	1.936	12.37	0.039	(0.020, 0.067)	0.084	(0.044, 0.146)
	30 - 39	1.578	11.85	0.012	(0.006, 0.020)	0.024	(0.012, 0.042)
	40 – 49	1.545	17.49	0.006	(0.003, 0.009)	0.012	(0.007, 0.019)
	50 – 64	2.592	57.74	0.005	(0.003, 0.006)	0.009	(0.007, 0.012)
	65 – 74	1.014	15.91	0.002	(0.001, 0.004)	0.004	(0.003, 0.007)
	≥75	0.391	7.51	0.002	(0.001, 0.004)	0.004	(0.002, 0.008)
Female	18 – 29	1.868	9.86	0.031	(0.015, 0.057)	0.067	(0.032, 0.124)
	30 - 39	1.544	31.57	0.034	(0.023, 0.048)	0.070	(0.048, 0.100)
	40 – 49	1.540	44.26	0.020	(0.015, 0.027)	0.042	(0.030, 0.056)
	50 – 64	2.670	77.69	0.008	(0.006, 0.010)	0.017	(0.013, 0.021)
	65 – 74	1.135	46.27	0.007	(0.005, 0.009)	0.014	(0.010, 0.018)
	≥75	0.542	19.88	0.004	(0.002, 0.006)	0.008	(0.005, 0.012)

Key: CI=Confidence Interval; LB=Lower Bound; O/E=Observed versus Expected; PE=Point Estimate; PY=Person years; RP=Reporting Percentage; US=United States.

a: Exposure in the US to 30 November 2021. Source: CDC (2021) for the US. Centers for Disease Control and Prevention, COVID data Tracker Website-https://covid.cdc.gov/covid-data-tracker

b: Counts included cases with events of interest that occurred within the risk window (1-42 days), and cases where time-to-onset was 0 or not reported.

c: Background Incidence Rate source: ACCESS (data FISABIO, 2018 – ACCESS report June 2021)

d: Poisson exact confidence interval (95% CI).

A review of the results for the US broad analysis (applying the assumption of a 100% reporting percentage and point estimate Incidence Rate) and the sensitivity analysis (applying the assumption of a 50% reporting percentage and lower bound incidence rate) showed an O/E ratio of <1 across all age-groups.

PRAC rapporteur comment:

Results of the O/E analyses could not be performed specifically for severe hypertension. However, analysis for hypertension in general does not indicate a concern.

MAHs conclusion

Based on review of the totality of the data that included double blind-placebo controlled clinical trials, cases from GMS Global Safety Database (solicited and unsolicited spontaneous reports), results from O/E

analyses and literature review, there is insufficient evidence to support a causal association between serious hypertension and the use of Ad26.COV2.S vaccine. Key factors supporting this conclusion include the finding that most of the cases of serious hypertension were confounded with concurrent or historical risk factors, or anxiety related reactions, the absence of imbalance from randomized double-blind Phase 3 Clinical Studies involving a large number of subjects, and O/E ratios well below 1 for all age groups as well as in sensitivity analyses. The results from the current analysis did not support a causal association of hypertension and use of Ad26.COV2.S vaccine. Ongoing routine pharmacovigilance activities are deemed sufficient to monitor events of hypertension.

Rapporteur assessment comment:

Clinical studies have not identified significant safety concerns regarding hypertension.

In the global safety database 678 cases of severe hypertension were detected, covering 656 cases from spontaneous reports.

Of note, almost half of the cases have been reported from one country, i.e. the Philippines were blood pressure measurements are part of the routines in the frame of the vaccination program. Cases were reported as increased BP (n=311), 13 cases referred to hypertension, and 1 case to hypertensive heart disease. Seven cases were fatal. Many of the reported cases have no information regarding blood pressure before vaccination and are lacking other information regarding medical history, show a very short TTO with start on the same day of vaccination and resolved later on.

The other 353 cases stem from other parts of the world. The most frequently reported events were hypertension (n=231 events), increased blood pressure (n=70 events), and hypertensive crisis (n=32 events). BP noted post-vaccination corresponded to Grade 3 in 114 cases, Grade 2 in 32 cases, Grade 1 in 10 cases. About 40% of the cases occurred within 2 days after vaccination. 12 events were fatal with either insufficient information regarding medical history or concurrent underlying diagnoses as confounders which might have caused the event. Events occurred in 14 cases together with anxiety (short TTOs), in 12 cases together with pregnancy (3rd trimester) and in 78 cases together with thromboembolic events. Remaining cases lacked either information regarding medical history or were confounded by other risk factors.

Literature study did not identify a clearly described association between the vaccine and hypertension.

Results of the O/E analyses could not be performed specifically for severe hypertension. However, analysis for hypertension in general does not indicate a concern.

Thus, no new safety concern is detected based on the currently available data regarding hypertension after vaccination with the Janssen Covid-19 vaccine.

The MAH should continue monitoring hypertension and severe hypertension via routine pharmacovigilance activities.

Autoimmune hepatitis

Narratives, based on all available information, for each of the 6 cases of new onset of AIH are provided below.

Cases are ordered according to the Revised Original Pretreatment Scoring System of the International Autoimmune Hepatitis Group (Table 1; Czaja 2008). A pretreatment aggregate score greater than 15 represents a definitive diagnosis of AIH and a score between "10" and "15" represents a probable diagnosis.

The diagnostic scoring for each of the 6 spontaneous cases did not exceed a score of "7" ("7" [n=1], "5" [n=1], "4" [n=1], and "2" [n=3]).

Thus, none of the cases met the diagnostic criteria of definitive (score: >15) or probable (score: 10-15) AIH.

Table 1: Revised Original Pretreatment Scoring System of the International Autoimmune Hepatitis Group*

Component	Result	Points	Component	Result	Points
Sex	Female	+2	HLA	DR3 or DR4	+1
AP:AST (or ALT) ratio	>3	−2	Immune disease	Thyroiditis, colitis, others	+2
	<1.5	+2			
γ-globulin or IgG level above normal	>2.0	+3	Other markers	Anti-SLA, actin, LC1, pANCA	+2
	1.5-2.0	+2			
	1.0-1.5	+1			
	<1.0	0			
	>1:80	+3			
ANA, SMA, or anti-LKM1 titers	1:80	+2	Histological features	Interface hepatitis	+3
	1:40	+1		Plasmacytic	+1
	<1:40	0		Rosettes	+1
				None of above	−5
				Biliary changes	−3
				Other features	−3
AMA	Positive	−4	Treatment response	Complete	+2
Viral markers	Positive	−3		Relapse	+3
	Negative	+3			
Drugs	Yes	−4	**Pretreatment aggregate score:**		
	No	+1	**Definite diagnosis >15**		
Alcohol	<25g/day	+2	**Probable diagnosis 10-15**		
	>60g/day	−2			

Abbreviations: AP, alkaline phosphatase; ALT, alanine aminotransferase; AMA, antimitochondrial antibody; ANA, antinuclear antibody; anti-LC1, antibody to liver cytosol type 1; anti-LKM1, antibodies to liver/kidney microsome type 1; anti-SLA, antibody to soluble liver antigen; AST, aspartate aminotransferase; HLA, human leukocyte antigen; IgG, immunoglobulin G; pANCA, perinuclear anti-neutrophil cytoplasmic antibodies; SMA, smooth muscle antibody.

*Adapted from Alvarez et al.[2]

Source: Czaja 2008

Diagnostic score of "7" (n=1):

AER #4.1(b)

This spontaneous report received from a patient via a Regulatory Authority [4.1(b)] ID 4.1(b) concerns a 58-year-old female who was diagnosed with AIH 39 days after receiving Ad26.COV2.S vaccine. The patient was an ex-smoker and social drinker with body mass index (BMI) of 28.9. Medical history included fatty liver and hypothyroidism since childhood. She experienced headache, diarrhea, vomiting and sore throat 4 days after vaccination. Laboratory results showed negative COVID-19 and Streptococcus test, and high liver enzymes. Liver scan was normal. The patient developed severe jaundice 19 days post vaccination. Her health deteriorated 2 weeks later. Symptoms included chills, diarrhea, fever, vomiting, fatigue, delusion, and confusion. Liver biopsy showed AIH due to non-alcoholic cirrhosis. Other laboratory results were not provided. She was hospitalized for 8 days. Treatment included prednisone and azathioprine. The patient developed diabetes due to prednisone and was on insulin treatment. Outcome of AIH was not reported. The AIH score is 7 (+2 for female gender, +2 for immune disease for hypothyroidism, +3 liver biopsy showed AIH), the report does not meet diagnostic criteria of definitive (Score >15) or probable AIH diagnosis (Score 10-15). The case reported AIH 39 days post vaccination in a 58-year-old female patient. Liver biopsy showed AIH due to non-alcoholic cirrhosis. Pre-existing fatty liver and autoimmune disorder hypothyroidism may have contributed to the event onset. Considering the temporal relationship of 39 days after vaccination and the finding of cirrhosis, the causality with the vaccination to the events are considered unlikely. Of note, previously reported AER #4.1(b) was identified on 31 January 2022 as a duplicate of AER#4.1(b) Thus, after merging of case data in the global safety database, all details concerning this serious adverse event (SAE) of AIH are subsumed under AER #4.1(b)

Rapporteur assessment comment:

The patient developed first symptoms 4 days after the vaccination, which worsened day 19 post vaccination, and received the diagnosis of AIH 39 days after vaccination. Of note, the biopsy showed signs of non-alcoholic liver cirrhosis, hinting to the fact of a longer ongoing hepatic process. The fact that the patient shows hypothyroidism may be a hint that the patient is at higher risk for AIH, although the exact reason for hypothyroidism is not described. Diagnosis criteria fulfil a possible AIH case. Based on the already abundant hepatic changes, ie. cirrhosis, it cannot be excluded that AIH was ongoing before the vaccination, and may have, besides NAFLD, led to the observed hepatic changes. Thus, a clear causality cannot be concluded in this case.

Diagnostic score of "5" (n=1):

AER #4.1(b)

This spontaneous report received from a physician via a Regulatory Authority [EMEA EVHUMAN NLP, 4.] concerns a 50-year-old female who experienced acute hepatitis, AIH, rash and headache requiring hospitalization 5 days after receiving the Ad26.COV2.S vaccine. No past medical history or concurrent conditions were reported. Laboratory data with unknown dates showed alanine aminotransferase (ALT) 1400 and 544, bilirubin 100 and 25, biopsy (date not reported) was suggestive of AIH and no fibrosis. Treatment was not reported. The patient had not recovered from the events. The AIH score is 5 (+2 female gender, +3 for histological feature of hepatitis), thus the report does not meet diagnostic criteria of definitive (Score >15) or probable AIH diagnosis (Score 10-15). The essential case information including the patient's medical history, concurrent conditions, concomitant medications, detailed workup and treatment are missing in this case, which preclude a meaningful medical assessment. However, considering time to onset of 5 days after vaccination and no other alternative etiologies identified, the causality of the vaccine cannot be excluded.

Rapporteur assessment comment:

This case with a short TTO of 5 days after vaccination is lacking medical history and also concomitant medication, which makes the case difficult to assess.

Diagnostic score of "4" (n=1):

AER #4.1(b)

This spontaneous report received from a health care professional via a Regulatory Authority [4.1(b) ID 4.1(b)] concerns a 35-year-old male who experienced AIH and primary sclerosing cholangitis requiring hospitalization 29 days after receiving the Ad26.COV2.S vaccine. Concurrent conditions included Grave's disease. Concomitant medications included levothyroxine. Following vaccination, the patient experienced symptoms of body aches, headache, insomnia, high blood pressure and pulse, gastrointestinal issues, fatigue, abdominal pain, rapid weight loss, loss of appetite, chromaturia, fever, malaise, and jaundice. Laboratory test showed increased alkaline phosphatase (ALP; 695), aspartate aminotransferase (AST; 825), ALT (1358), bilirubin, globulin (5.0), platelet and white blood cell (WBC) count. He was diagnosed with ulcerative colitis by colonoscopy, common bile duct blockage with cholecystitis and hepatitis by endoscopic retrograde cholangiopancreatography (ERCP) 27 days post vaccination. A stent was placed and a cholecystectomy was performed. He was diagnosed as overlap syndrome of AIH and primary sclerosing cholangitis by liver biopsy 2 days later. Prednisone was started and infliximab was planned. The patient had not recovered from the events.

The AIH score is 4 (+2 for AP:AST [or ALT] ratio <1.5, +3 for globulin of 5 [>2], +2 for autoimmune

disease [Graves, ulcerative colitis], -3 for histological features [other features: primary sclerosing cholangitis]), the report does not meet diagnostic criteria of definitive (Score >15) or probable AIH diagnosis (Score 10-15). The case reported AIH, ulcerative colitis and primary sclerosing cholangitis in a patient with underlying Grave's disease and ulcerative colitis, suggesting a possible role of autoimmunity and considered as a risk factor for AIH (John Hopkins Medicine 2022). Primary sclerosing cholangitis is a chronic progressive condition with known association to ulcerative colitis, almost half can be asymptomatic at the time of diagnosis while others already have advanced disease. Considering risk factor of multiple autoimmune disorders, the causal relationship with vaccination to the event is considered unlikely.

Rapporteur assessment comment:

This case with symptom start 27 days after vaccination presents with several risk factors comprising different ongoing autoimmune diseases, hinting to a higher risk profile for AIH in this patient. The view of the MAH is endorsed that the causal association with the vaccine is rather unlikely.

Diagnostic score of "2" (n=3):

AER #4.1(b)

This spontaneous report received from a patient via a Regulatory Authority [4.1(b)] ID 4.1(b) concerns a 52-year-old female who experienced life threatening AIH, liver injury, liver transplant, hepatitis B reactivation, biopsy liver abnormal, condition aggravated, liver function test abnormal and acute hepatic failure 7 days after receiving the Ad26.COV2.S vaccine. Concurrent conditions included Tegaderm (transparent film dressing) allergy, hepatitis B, chronic rheumatoid arthritis, and asthma. The patient experienced nausea when treated with ampicillin, itching when treated with chlorhexidine, and stomachache when treated with acetylsalicylic acid. Concomitant medications included diclofenac, ergocalciferol, hydroxychloroquine phosphate, ibuprofen, and montelukast sodium. Liver biopsy was performed 22 days post vaccination, but results were not provided. The patient had a liver transplant 41 days post vaccination. She had recovered from the events on an unspecified date. The AIH score is 2 (+2 for female gender, +2 for autoimmune disease [chronic rheumatoid arthritis], +2 for treatment response complete, +3 for histological features [biopsy liver abnormal, on conservative assessment], -4 for drugs [diclofenac and ibuprofen], -3 for hepatitis B). The report does not meet diagnostic criteria of definitive (Score >15) or probable AIH diagnosis (Score 10-15). Potential risk factors include concurrent hepatitis B, chronic rheumatoid arthritis, asthma, history of allergies, concomitant medications of diclofenac (Cleveland Clinic 2022), and ibuprofen (National Institute of Diabetes and Digestive and Kidney Diseases 2018). Due to concurrent viral hepatitis, autoimmune disorder, and concomitant medication, contributory role of these risk factors cannot be ruled out and the causal relationship with vaccination to the event is considered unlikely.

Rapporteur assessment comment:

This case with symptom start 7 days after vaccination is confounded by concurrently ongoing viral hepatitis, and other autoimmune disorder, as well as multiple concomitant medication. The patient is liver transplanted. The AIH score is rather low. A causal relationship with the vaccine is rather unlikely.

AER #4.1(b)

This spontaneous report received from a patient concerns a female of unspecified age who experienced AIH 3 days after receiving Ad26.COV2.S vaccine. Medical history, concurrent conditions, concomitant

medications were not reported. The patient had elevated ALT (1500), and unspecified hepatic enzyme over 1300. Detailed workup, treatment and outcome were not provided. The AIH score is 2 (+2 points for female gender, and no other scoring parameters available), the report does not meet diagnostic criteria of definitive (Score >15) or probable AIH diagnosis (Score 10-15). The essential case information including age, medical history, concurrent conditions, concomitant medications, detailed workup, treatment, and outcome are missing in this case, which precludes any meaningful medical assessment.

Rapporteur assessment comment:

This case with symptom start 3 days after vaccination is scarcely described regarding medical history and diagnosis work-up. Thus, causality cannot be assessed.

AER #4.1(b)

This spontaneous report received from a health care professional via a Regulatory Authority [4.1(b)] ID 4.1(b) concerns a 58-year-old female patient who experienced abdominal pain 4 days after receiving the Ad26.COV2.S vaccine and was diagnosed with AIH (life-threatening) approximately 4 months after vaccination. Medical history, concurrent conditions, concomitant medications were not reported. Biopsy, computer tomography (CT), and endoscopy were performed but results were not reported. Treatment information was not reported. The patient had not recovered from the event. The AIH score is 2 (+2 for female gender and no other scoring parameters available), the report does not meet diagnostic criteria of definitive diagnosis (Score >15) or probable AIH diagnosis (Score 10-15). The essential case information including medical history, concurrent conditions, concomitant medications, detailed workup, and treatment, are missing in this case, which precludes any meaningful medical assessment.

In summary, none of the 6 cases reporting AIH met the diagnostic criteria of definitive or probable AIH. Based on the review of evidences from these cases, there was insufficient evidence to conclude that AIH is causally associated with the use of Ad26.COV2.S vaccine. This topic will continue to be monitored through routine pharmacovigilance activities.

Rapporteur assessment comment:

This case with symptom start 4 days after vaccination and diagnosis of AIH 4 months after vaccination is characterized by scarce description regarding medical history and diagnosis work-up and thus difficult to assess regarding causality

Rapporteur overall assessment comment (AIH):

Presented cases are characterized by missing information regarding missing information or additional underlying risk factors/confounders for AIH. A causal association between the vaccine and AIH is thus not confirmed. A continuous monitoring of AIH by routine pharmacovigilance activities is endorsed.

7. Comments from Member States

Member states' comments:

A total of three MS comments are received.

MS1 and the **MS2**: We fully endorse the PRAC Rapp assessment and have no further comments.

MS3

Autoimmune flares

Although agreeing with the PRAC Rapp assessment report overall, i.e., refuting the signal of flare of autoimmune disorders following vaccination with Ad26.COV2.S in the current PSUR, MS3 considers that the potential risk of exacerbation (flare-up) of a pre-existing auto-immune (AI) or inflammatory disorder needs to be closely monitored also in the future PSURs for each COVID-19 vaccine. Therefore, MS3 suggests requesting the following from the MAH:

- A cumulative review of exacerbation (flare-up) of pre-existing autoimmune/inflammatory disorders to be presented in the next PSUR including data from, at least, scientific literature and the post-marketing cases. This should include a tabulated case summary including the following columns: Case ID, Eudravigilance Case ID, PTs, Patient Age, Patient Gender, First Dose to Onset, Medical History, Concomitant Medications, Case Comment, information dose, WHO causality assessment and the reasoning for the causality category.

- MAH should present full case narratives of exacerbation (flare-up) of pre-existing autoimmune/inflammatory disorder in patients with known pre-existing such disorder at steady stage and without other reported alternate aetiology or contributing factor. The full case narratives should at least contain; time from First Dose to Onset (days) of the exacerbation (flare-up), time from last dose to onset, Medical History (including date first symptoms and diagnostic of AI/Inflammatory disorders) and current medications.

- If the MAH considers that an update to the product information is needed, suggestion for SmPC text and corresponding frequency calculations should be presented, as appropriate. The MAH should also consider based on the updated information in the next PSUR whether the current risk characterization of the missing information category "Use in Subjects with Autoimmune or Inflammatory Disorders" should be updated.

MS3 further states that the plausible mechanism of action for flare-up of AI/inflammatory disorders post vaccination is unknown. Thus, the rationale could also be applied to all marketed COVID-19 vaccines and therefore, MS3 also proposes to harmonize the safety monitoring for this potential risk across others COVID-19 vaccines.

Neuralgic Amyotrophy

MS3 notices the conclusion of the PRAC Rapp :

"The O/E analyses were <1. Despite some cases with a temporal relationship to vaccination, and thereby assessed as possible, it is at this stage agreed that there is insufficient evidence to allow conclusion on causality. Routine PhV is also agreed."

Three case reports of neuralgic amyotrophy (NA) have been reviewed by an independent expert in neurology, who confirmed the diagnostic, for 2 of them, of NA. Nevertheless, according the MAH, none of them met the diagnostic criteria. These two cases are presented below:

- 4.1(b) - 58 years old female, history of hereditary sensory-motor neuropathy:

o TTO: 10 days

o Clinical symptoms: Quite violent pain opposite the scapula, then very severe complete deficit of the extensors of the fingers and wrist as well as of the left long supinator

o Diagnosis: neuralgic amyotrophy syndrome in a form involving the left C6 root and radial nerve,

occurring on known and unchanged sequelae of previous involvement

o Evolution: unknown

- 4.1(b) - 57 years old male, no medical history:

o TTO: 22 days

o Clinical symptoms: Atrophying deficit of the right circumflex muscle (vaccinated arm), hyperalgesic.

o Diagnosis: At 4 months the patient presents signs of severe neurogenic suffering in the right deltoid, without signs of recovery. Slowing of the motor conduction velocity of the ulnar never at the elbow, as well as of the sensitive conduction of the right median nerve on the IV. Thus benign postural damage of the ulnar nerve at the elbow. Sequelae of partial post-traumatic neuropathy of the right median nerve or carpal tunnel syndrome. Very severe impairment of the right circumflex with active denervation without voluntary motor function: neuralgic amyotrophy syndrome

o Evolution: unknown

Since the 18th October, 3 other case reports of NA have been analyzed, with a temporal relationship to vaccination (1 and 10 days).

Today, Vigilyze contains 30 cases of NA (PT) which occurred with Ad26.Cov2.S, associated with a disproportionality (IC025 2.1). In Eudravigilance, there is 20 cases of NA (PT) which occurred with Ad26.Cov2.S, associated with a disproportionality (ROR(-) 3.02).

Considering cases a temporal relationship to vaccination and thereby assessed as possible, MS3 thinks that it is too early to rule out the causality. MS3 suggests to continue to closely monitor this topic for the next PSUR with a cumulative review of all new cases and literature. The MAH should discuss of a update of the product information if necessary.

Rapporteur's comment:

Autoimmune flares

It is agreed with MS3 that a harmonized safety monitoring across all COVID-19 vaccines is of importance. In the current PSUR all the presented patient cases with autoimmune/inflammatory flares following vaccination were thoroughly assessed without strong signals of a causal relationship to vaccination. There were however, as stated above, limited information with respect to temporality, onset of symptoms, information on comorbidity, and other medications etc. for many of the cases. Further, in several cases, the symptoms included arthralgia, myalgia and fever, i.e., common general vaccination reactions rather than verified flare-up in an arthritis disease for example, speaking against a true disease flare.

The suggestion from MS3, to ask a similar question as for other covid-19 vaccines is endorsed; namely:

-The MAH should present an updated review of exacerbation (flare-up) of pre-existing autoimmune/inflammatory disorders in the next PSUR including data from the scientific literature, clinical studies and the post-marketing cases.

-A tabulated case summary of cases that have occurred after the cut off for the review within the current PSUSA should be presented, with the following columns: Case ID, Eudravigilance Case ID, PTs, Patient Age, Patient Gender, First Dose to Onset, Medical History, Concomitant Medications, Case Comment, information dose, WHO causality assessment and the reasoning for the causality category. All available information should be presented to help the review, including time from first dose to onset of the flare-up, time from last dose to onset, medical history (including date first symptoms and current medications, if available.

In the data presentation and overall discussion, cases from the current review and new cases should be clearly identified, to facilitate the review.

If also the next evaluation in the coming PSUR reaches the same conclusion as in the present one, namely that there is no indication of any causal association, further reviews of flare-up following Ad26.COV2.S vaccine in patients with autoimmune/inflammatory disorders would not seem warranted, and routine pharmacovigilance be sufficient.

Finally it should be noted that according to the RMP, "Use in Subjects with Autoimmune or Inflammatory Disorders" will be addressed in two planned observational post authorization safety studies (category 3; VAC31518COV4003 and VAC31518COV4001) with the aim to assess the safety of Ad26.COV2.S vaccine and with final reporting 2024. The MAH should comment on if any interim results regarding use in subjects with autoimmune or inflammatory disorders, especially on flare-ups, from these studies may be available and submit those if possible.

Neuralgic Amyotrophy

The update regarding cases of neuralgic amyotrophy that have been observed by MS3 and cases collected in Vigilyze and Eudrovigliance are acknowledged. The position of the MS is supported, i.e. that the MAH is requested to continue to closely monitor this topic in the next PSUR with a review of all new cases and literature. The MAH should discuss if an update of the product information is necessary.