JCOVDEN : Periodic safety update report assessment

25th February 2022 to 24th August 2022

This document consists of:

1. The PRAC assessment report of the JCOVDEN periodic safety update report (PSUR) covering the period 25th February 2022 to 24th August 2022, and;

2. The JCOVDEN PSUR itself.

The PSUR is a pharmacovigilance document intended to provide an evaluation of the risk-benefit balance of the medicinal product during the reference period mentioned above.

The objective of the PSUR is to present a comprehensive and critical analysis of the risk-benefit balance of the product, taking into account new or emerging safety information in the context of cumulative information on risk and benefits. The marketing authorisation holder is legally required to submit PSURs at defined time points after the authorisation of a medicinal product.

EMA's safety committee, the PRAC, assesses information in the PSUR to determine if there are new risks identified for a medicine and/or if its risk-benefit balance has changed. The outcome of this assessment is summarised in the PRAC assessment report of the PSUR.

The PSUR and the PRAC assessment report of the PSUR include information about **suspected** side effects, i.e. medical events that have been observed following the use of the vaccine, but which are not necessarily related to or caused by the vaccine itself. Information on suspected side effects should not be interpreted as meaning that the vaccine or the active substance causes the observed event or is unsafe to use.

Only a detailed evaluation and scientific assessment of all available data, as described in the PRAC assessment report of the PSUR, can determine the impact of new data on the benefits and risks of a medicine.

Further information on the safety of COVID-19 vaccines and on PSUR submission and assessment is available on the EMA website.

This document may contain redactions for commercially confidential information (CCI) and protected personal data (PPD) in accordance with applicable legislation and guidance.

EMA/PRAC/103506/2023
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC PSUR assessment report

Procedure no.: EMEA/H/C/PSUSA/00010916/202208

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

Period covered by the PSUR: 24/02/2022 To: 24/08/2022

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

Status of this report and steps taken for the assessment[1]			
Current step	**Description**	**Planned date**	**Actual Date**
☐	Start of procedure:	17 November 2022	17 November 2022
☐	PRAC Rapporteur's preliminary assessment report (AR)	16 January 2023	16 January 2023
☐	MS/PRAC members and MAH comments	15 February 2023	15 February 2023
☐	PRAC Rapporteur's updated assessment report following comments	2 March 2023	2 March 2023
☐	PRAC discussion	16 March 2023	16 March 2023
☐	ETF consultation	24 March 2023	24 March 2023
☐	CHMP consultation	30 March 2023	28 March 2023
☐	PRAC Rapporteur's 2nd updated assessment report following comments	4 April 2023	4 April 2023
☐	Oral explanation	N/A	N/A
☒	PRAC recommendation	14 April 2023	14 April 2023

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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]) (JCOVDEN).

2. Assessment conclusions and actions

This is the third Periodic Safety Update Report (PSUR) for COVID-19 vaccine Janssen (Ad26.COV2.S); covering data for the period from 25 February 2022 to 24 August 2022.

Ad26.COV2.S Janssen is indicated for active immunisation for the prevention of coronavirus disease-2019 in adults 18 years of age or older.

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

During the PSUR interval, a total of 128,582,300 doses of Ad26.COV2.S vaccine were estimated to have been distributed worldwide. Of these, a majority was distributed to ROW-countries and approximately 5,963,100 doses to the US and 1,524,000 doses to the EEA countries. Cumulatively, 52,7 mil doses were estimated to have been administered worldwide.

Changes of the product information have been made during this PSUR period including the inclusion in section 4.8 of the SmPC of small vessel vasculitis and facial paralysis.

No signal was ongoing during the reporting interval. Several signals were closed during the reporting interval including IgA nephropathy, facial paralysis, coronary artery disease including myocardial infarction (MI) and venous thromboembolism. Closing of the signal of IgA nephropathy and coronary artery disease including MI without further actions is endorsed based on the presented data. The latter has been subject to a dedicated review by the PRAC during Q2 2022. Facial paralysis and venous thromboembolism have been included in the product information, following previous reviews by the PRAC.

Furthermore, the MAH presented evaluations of neuralgic amyotrophy. No new safety concern is detected here. In addition, the MAH presented an updated analysis on cutaneous vasculitis. Recently, small vessel vasculitis has been added to the SmPC, section 4.8. After the data lock point, the MAH opened a safety signal based on the disproportionate reporting of vasculitis, particularly cutaneous vasculitis. The evaluation of this signal is ongoing and will be presented in the next PBRER.

During this PSUR reporting interval, the EU RMP has been updated to remove anaphylaxis as an important identified risk from the list of safety concerns (version 4.2).

The MAH also proposed to retire three follow up questionnaires (FUQ), namely for thrombosis with thrombocytopenia syndrome (TTS), venous thromboembolism (VTE), vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) and multisystemic inflammatory syndrome (MIS). This is endorsed, and the RMP can be updated at the next regulatory opportunity.

Following assessment of the current PSUR, a review of various AESIs, which have been reviewed repeatedly within monthly safety summary reports and PSURs, has not identified new safety concerns. Therefore, in depth presentation of new data for a number of AESIs is not warranted anymore, and it is suggested to remove several terms from the section AESI evaluations (see chapter issues to be addressed with the next PSUR). More detailed presentation is only needed if new information that can raise safety concerns is identified.

During the PRAC meeting in March 2023, some concerns were raised with respect to the conclusion that the benefit risk balance remains unchanged. The concerns were raised in the context of:

1. the well-established safety profile of this vaccine which includes serious adverse drug reactions (ADRs) that have been identified post marketing [i.e. TTS (frequency very rare), VTE (frequency rare), immune thrombocytopenia (ITP) (frequency not known), Guillain Barré syndrome (GBS) (frequency very rare), transverse myelitis (frequency not known), capillary leak syndrome (CLS) (frequency not known) and cutaneous small vessel vasculitis (frequency not known)],
2. the fact that the vaccine is based on the original Wuhan strain,
3. the epidemiological evolution of the virus, the available possibilities for prevention and treatment of a SARS-CoV-2 infection, and the current risks for serious outcomes of the disease.

It was also noted that the current PSUSA does not contain substantially new data on benefits or risks, in relation to the renewal procedure, which was concluded at the CHMP in December 2022. In this procedure, the benefit/risk profile was considered unchanged, and the conditional marketing authorisation (CMA) was switched into a full marketing authorisation based on the comprehensiveness of the pharmaceutical quality and clinical data. To further contextualise the concerns raised above, additional consultations with ETF and CHMP took place during the review of the current PSUR.

As outlined in the first updated assessment report (2 March 2023), the MAH informed the EMA on 17 February 2023 that the U.S. FDA had, on 14 Feb 2023, requested to update the JCOVDEN EUA fact sheet to include new warnings and precautions for myocarditis and pericarditis. At that time, the MAH stated that based on the totality of safety data available, there was insufficient evidence to establish a causal association between Ad26.COV2.S and the occurrence of cardiac inflammatory disorders (including myocarditis and pericarditis). An updated and detailed analysis was planned to be submitted in the upcoming PSUR with DLP 24 February 2023.

On 31 March 2023, the MAH submitted updated information on this topic, in the form of an Emerging Safety Issue (ESI). Following the FDA request, the MAH has performed a full analysis of the available safety data for myocarditis and pericarditis. The MAH concludes that data available up to the DLP for the next PSUR (24 February 2023) show an increase in the risk for myocarditis and pericarditis following Ad26.COV.S vaccination, particularly in males under the age of 40 in the first two weeks following vaccination, with the highest risk at 7 days. They also conclude that this suggests that there is a reasonable possibility of a causal association between Ad26.COV2.S and myocarditis and pericarditis. The MAH proposes to add myocarditis and pericarditis as an Important Identified Risk in the RMP, and states that it will be included as ADRs in the company core data sheet and that a warning text will be added. The MAH also proposes to submit an updated product information and RMP in the next PSUSA procedure (due for submission on 5 May 2023 – DLP 24 February 2023).

The PRAC notes that further analyses have been performed up to the DLP for the next PSUSA, and that the MAH has, based on these analyses, revised their conclusion regarding causality between myocarditis and pericarditis andAd26.COV2.S , and thereby concluded on a need for an update of the product information. Furthermore, their proposal to apply for an updated product information and RMP within the next PSUR is noted, but not agreed as the finalisation of the PSUSA is not due until September 2023. Myocarditis and pericarditis can be serious conditions, and therefore warrant prompt attention and review. As a consequence, the MAH should submit a Type II variation, as a follow up of the current PSUSA, for further assessment. This variation should also contain a discussion of benefits and risks of Jcovden, taking these new safety data into account, in relation to the current knowledge of safety and efficacy, including the epidemiological evolution of the virus.

Assessment of the data within the current PSUSA does not impact the balance between benefits and risks, and thus the benefit-risk balance remains unchanged. This conclusion is without prejudice to the further review and outcome of the requested type II variation.

3. Recommendations

Based on the PRAC 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).

This recommendation is without prejudice to the outcome of the requested type II variation on myocarditis and pericarditis.

4. Issues to be addressed in the next PSUR or as a post-authorisation measure (PAM)

- By 17 April 2023, the MAH should submit a Type II variation to address their new conclusion that myo/pericarditis is an important identified risk for Jcovden. This variation application should include detailed analyses of available safety data on this topic, a proposal for updates of the product information and an updated RMP. Furthermore, a discussion of the balance of benefits and risks of this vaccine, taking these new safety data into account, and in relation to the current knowledge of safety and efficacy, including the epidemiological evolution of the virus, should also be provided.

The MAH(s) should also address the following issues in the next PSUR:

- After the reporting interval, a paper based on epidemiological US-based was published where the risk for postural orthostatic tachycardia syndrome (POTS) after covid-19 vaccination was investigated. *Kwan, A.C., Ebinger, J.E., Wei, J. et al. Apparent risks of postural orthostatic tachycardia syndrome diagnoses after COVID-19 vaccination and SARS-Cov-2 Infection. Nat Cardiovasc Res (2022).* For the next PSUR, the MAH is asked to discuss this issue.
- The following terms are no longer needed to be presented in depth in the chapter on "evaluations of AESIs" since no signals have been identified since launch, or since some of these already are important identified risks in the RMP. These items should be only comprehensively discussed in the upcoming PSURs in case that changes in the reporting patterns and/ or a novel signal are detected. For the important identified risks, these should be addressed as appropriate within those parts of the PSUR:
    1. Hepatic AESIs, convulsions, sensorineural hearing loss, acute kidney failure, DIC, transverse myelitis, acute aseptic arthritis
    2. The section 'Update on special patient populations', i.e. pregnancy/breastfeeding; Use in immunocompromised patients; Use in patients with autoimmune or inflammatory disorders; Use in frail patients with comorbidities (e.g., chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders should only be included and discussed in the PSUR if the reporting pattern changes and/or there is a safety issue/signal.
    3. The vaccination stress/anxiety related ADRs are considered well documented and adequately managed in clinical practice, and therefore could be removed from detailed presentation in future PSURs.
    4. Severe cutaneous adverse reactions have been evaluated in previous procedures, but there are some time periods which have not been reviewed. For the next PSUR, the period 25 February 2022 to 24 February 2023 should be specifically analysed, inclusive high-level analysis of post-marketing cases and the literature regarding SCAR.

5. PSUR frequency

☒Changes of PSUR frequency are proposed

The current frequency of submission should be changed from **6** months to 1 year at the first possibility. The list of Union reference dates (EURD) should be updated accordingly.

The next PSUR should be submitted according to the current EURD list (i.e. **next DLP: 24 February 2023** and next submission date: 5 May 2023). The PSUR cycle will be updated for the **following PSUR** which should submitted with a **DLP of 24 February 2024**.

6. Other considerations

N/A

Annex: 2nd updated PRAC Rapporteur assessment comments on PSUR

1. PSUR Data

1.1. Introduction

This Periodic Safety Update-Single AR for JNJ-78436735(Ad26.COV2.S), herein referred to as Ad26.COV2.S, summarises the safety data obtained by the Company from worldwide sources for the reporting period of 25 February 2022 to 24 August 2022. This is the third Periodic Safety Update-Single AR for JNJ-78436735(Ad26.COV2.S).

Ad26.COV2.S is indicated for active immunisation for the prevention of coronavirus disease-2019 (COVID-19) caused by SARS-CoV-2 in adults greater than or equal to 18 years of age.

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. Following vaccination, the spike protein is expressed and stimulates an immune response.

Ad26.COV2.S is supplied as a colourless to slightly yellow, clear to very opalescent single dose suspension for intramuscular injection. One dose of Ad26.COV2.S contains 5x1010 virus particles in 0.5 mL. Ad26.COV2.S is produced in the PER.C6® TetR Cell Line and by recombinant deoxyribonucleic acid technology.

No changes to the product information have been proposed by the MAH as a part of the submission of this PSUR.

1.2. Worldwide marketing authorisation status

Worldwide Marketing Authorisation Status
The International Birth Date (IBD) of Ad26.COV2.S is based on the first regulatory approval in Bahrain on 25 February 2021. Ad26.COV2.S is authorised in 108 countries/territories and import licences have been granted in 20 countries/territories worldwide. In addition, Ad26.COV2.S obtained an Emergency Use Listing by the World Health Organization.

Table 1: List of Countries/Territories Where Ad26.COV2.S is Authorised (n=108)

Algeria	Czech Republic	Kuwait	Qatar
Antigua and Barbuda	Denmark	Laos	Romania
Argentina	Egypt	Latvia	Rwanda
Australia	Estonia	Lebanon	Saudi Arabia
Austria	Ethiopia	Lichtenstein	Sierra Leone
Bahamas	Finland	Lithuania	Slovakia
Bahrain	France	Luxembourg	Slovenia
Bangladesh	Gabon	Madagascar	Solomon Island
Belgium	Gambia	Malaysia	Somalia
Belize	Georgia	Malta	South Africa
Bolivia	Germany	Mauritius	South Sudan
Botswana	Ghana	Mexico	Spain
Brazil	Greece	Moldova	Sudan
Bulgaria	Guatemala	Mozambique	Sweden
Burundi	Guinea	Nepal	Switzerland
Cabo Verde	Guyana	Netherlands	Syria
Cameroon	Haiti	New Zealand	Thailand
Canada	Hungary	Nicaragua	Trinidad and Tobago
Central African Republic	Iceland	Nigeria	Tunisia
Chad	India	Norway	Uganda
Chile	Indonesia	Oman	Ukraine
Colombia	Ireland	Panama	United Arab Emirates
Comoros	Italy	Papua New Guinea	United Kingdom (Great Britain)
Congo	Jamaica	Peru	United States
Cote d'Ivoire	Japan	Philippines	Vanuatu
Croatia	Kenya	Poland	Vietnam
Cyprus	Korea	Portugal	Zimbabwe

Key: n=Number

Table 2: List of Countries/Territories Where Ad26.COV2.S is Granted Import Licences (n=20)

Angola	Eswatini	Malawi	Sao Tome and Principe
Benin	Guinea-Bissau	Mali	Senegal
Burkina Faso	Lesotho	Mauritania	Tanzania
Congo (Democratic Republic of)	Liberia	Namibia	Togo
Djibouti	Libya	Niger	Zambia

Key: n=Number

Rapporteur assessment comment:

The IBD of Ad26.COV2.S is based on the first regulatory approval in Bahrain on 25 February. In the EU Ad26.COV2.S was authorized on 11/03/2021. AD26.COV2.S is authorised in total 108 countries/territories worldwide and import licences is granted in 20 countries/territories.

In the last PSUR, it was stated that AD26.COV2.S was authorised in total 128 countries/territories, in this PSUR the MAH has specified that AD26.COV2.S is authorized in 108 countries/territories and that 20 countries/territories have granted import licences.

1.3. Overview of exposure and safety data

1.3.1. Actions taken in the reporting interval for safety reasons

The significant actions taken for safety reasons during the period covered by this report are presented below in Table 3.

Table 3: Significant Actions Taken for Safety Reasons During the Reporting Period

Date	Country/Territory	Issue	Action Taken
29 March 2022	EU	Completion of an additional pharmacovigilance activity mentioned in the EU RMP version 3.1 (approved on 13 January 2022 via procedure: EMEA/H/C/005737/II/0029).	On 29 March 2022, a grouping of Type II-variations (EMA/H/C/5737/II/0047/G) covering the final study reports of 5 non-clinical TTS characterisation studies regarding Ad26.COV2.S was submitted.
30 March 2022	EU	Completion of an additional pharmacovigilance activity mentioned in the EU RMP version 3.1 (approved on 13 January 2022 via procedure: EMEA/H/C/005737/II/0029).	On 30 March 2022, a grouping of Type II-variations (EMA/H/C/5737/II/0048/G) covering the final study reports of 4 clinical TTS characterisation studies regarding Ad26.COV2.S and an updated EU RMP (version 4.1) was submitted to EMA.
12 April 2022	EU	Request in final PRAC outcome for the SSR(EMEA/H/C/005737/MEA/014.8) covering 01 November 2021 to 15 January 2022 to include cutaneous small vessel vasculitis as an ADR in the EUPI	PRAC request to include small vessel vasculitis with cutaneous manifestations as an ADR in the EUPI. EMA proposed to change the wording to "cutaneous small vessel vasculitis" in an email dated 15 March 2022. Type IB variation submitted to EMA on 12 April 2022. Notification is received on 19 April 2022 (EMA/H/C/5737/IB/0051). Submissions to other HA's were made in line with local requirements.
05 May 2022	EU	A pooled analysis of the double-blind phase of 5 clinical trials conducted by the MAH at the time of the preparation of the PBRER (period: 25 August 2021 to 24 February 2022), showed a numerical imbalance between Ad26.COV2.S vaccine and placebo for facial paralysis/Bell's palsy. A cumulative assessment of available safety data has been carried out as a result of this imbalance and is presented in the PBRER with the reporting period of 25 August 2021 to 24 February 2022. Based on the totality of the data, the MAH has concluded there is a reasonable possibility of a causal association between Ad26.COV2.S vaccine and facial paralysis/Bell's palsy.	The product information was amended to include facial paralysis (including Bell's palsy) as an adverse reaction and was included in the PBRER submission (EMEA/H/C/PSUSA/00010916/202202) performed on 05 May 2022.
05 May 2022	US	EUA fact sheet updates for prominent placement for TTS warning and limitation of use of Ad26.COV2.S vaccine.	FDA reached out to Janssen on 27 April 2022 with proposed updates to the HCP and RCG fact sheets. The final documents were submitted to the EUA, which implemented the placement of warning for TTS at the beginning of the HCP fact sheet and limitation of use. RCG fact sheet was updated in accordance. FDA provided approval in form of updated LoA for the EUA on the same date. HA submissions in other countries/territories were made in line with local requirements. The Company did not consider this an ESI.
09 May 2022	TUN	Suspension of the use of "Johnson & Johnson" COVID-19 vaccine by the Health authority.	Provisional suspension, by precautionary measure, the use of the specialty Ad26.COV2.S vaccine given the occurrence of adverse effects and following the latest US FDA recommendation to limit the use of the "Johnson & Johnson" coronavirus vaccine. The Exceptional Marketing Authorisation previously issued is not suspended.
20 June 2022	Japan	Externally identified SSI.	PMDA requested that "immune mediated and neuroinflammatory events" are included as an important potential risk in the J-RMP. Consequently, a precaution statement is included in the initial Japan PI, approved by the MHLW on 20 June 2022, as a risk minimisation measure for this J-RMP important potential risk. HA notifications in other countries/territories were made in line with local requirements. The Company did not consider this an ESI.
30 June 2022	EU	A pooled analyses of safety data from Phase 1, 2 and 3 clinical studies with Ad26.COV2.S to assess the reactogenicity profile and the frequency of adverse events after primary vaccination with Ad26.COV2.S and after homologous boosting with Ad26.COV2.S in adults aged ≥18 years is submitted to EMA as a Type II variation.	The product information was amended (EMEA/H/C/005737/II/0060) in accordance with the results obtained from pooled analyses of safety data.

Key: ADR=Adverse Drug Reaction; API=Active Pharmaceutical Ingredient; AMI=Acute Myocardial Infarction; AR=Aggregate Report; CAD=Coronary Artery Disease; COVID-19=Coronavirus Disease-2019; EMA=European Medicines Agency; EMEA=European Medicines Evaluation Agency; ESI=Emerging Safety Issue; EU=European Union; EUA=Emergency Use Authorisation; EUPI=European Union Product Information; FDA= Food and Drug Administration; GMP=Good Manufacturing Practice; HA=Health Authority; HC=Health Canada; HCP=Health Care Professional; J-RMP=Japan-Risk Management Plan; LoA=Letter of Acceptance; MAH=Marketing Authorisation Holder; MHLW=Ministry of Health, Labour and Welfare; MI=Myocardial Infarction; O/E=Observed versus Expected; PBRER= Periodic Benefit-Risk Evaluation Report; PI=Package Insert; PM=Product Monograph; PMDA=Pharmaceuticals and Medical Devices Agency; PRAC=Pharmacovigilance Risk Assessment Committee; RCG=Recipients and Caregivers; RMP=Risk Management Plan; SSI=Significant Safety Issue; SSR=Summary Safety Report; TTS=Thrombosis With Thrombocytopenia Syndrome; US=United States; NZ=New Zealand

Rapporteur assessment comment:

The MAH has described regulatory actions taken globally during the period, which is noted.

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 June 2022. Significant changes to the CCDS (ie, CCSI) made within the reporting interval are listed in the table below.

Table 4: Significant Changes to the Ad26.COV2.S CCDS During the Reporting Period

CCDS Version and Date	CCDS Section	Description of Change(s)
CCDS V12 Version Date: 14 June 2022	Dosage and Administration, Adverse Reactions, Clinical Studies.	The CCDS has been revised to include information from COV2008, COVBOOST, and MIXNMatch studies to support the booster dose as follows: -support 6-month dosing interval for the homologous booster dose (COV2008); -additional information from COV2008, COVBOOST and MIXNMatch studies to support heterologous booster following primary vaccination with an mRNA COVID-19 vaccine; -additional safety information related to an increased trend in reactogenicity seen after a heterologous booster dose with an mRNA COVID-19 vaccine; -inclusion of information in relation to booster dose after AstraZeneca COVID-19 vaccine (COVBOOST); -inclusion of information in relation to booster dose after CoronaVac (RHH-001 Study).
CCDS V13 Version Date: 28 June 2022	Adverse Reactions	Safety pooling for the primary vaccination Addition of Facial paralysis (including Bell's palsy) as a post-marketing adverse reaction. Addition of Venous thromboembolism as a post-marketing adverse reaction.

Key: CCDS=Company Core Data Sheet; COVID-19=Coronavirus Disease-2019; mRNA=Messenger Ribonucleic Acid; V=Version

Rapporteur assessment comment:

The MAH has described changes to the reference information during the period, which is noted.

The information that has been updated in the CCDS is in agreement to the updates regarding Bell´s palsy and homologous boosting that have been made to the product information in the EU during the period covered by this report.

1.3.3. Estimated exposure and use patterns

Cumulative subject exposure in clinical trials

Overall, an estimated 82,152 healthy subjects have been enroled in the Ad26.COV.S clinical programme, of which approximately 68,611 subjects have received Ad26.COV.S in the Company-sponsored interventional clinical trials (see Table 5). Of these, 580 subjects were exposed to Ad26.COV.S in the Phase 1 trials, 935 in a Phase 1/2a trial, 1,886 in the Phase 2 trials, 537 in the Phase 2a trial, and over 64,673 in the Phase 3 trials. Additionally, 16,142 subjects were exposed to Ad26.COV.S in the pre-approval access programmes, and 751,922 in the other studies.

Table 5: Estimated Cumulative Subject Exposure From Clinical Trials

Treatment	Number of Subjects
Ad26.COV2.S	68,611
Comparator	N/A
Placebo	39,370

Note: Number of subjects exposed to at least 1 study vaccine, recorded in the study databases up to cut-off date (24 August 2022).
Trials included: VAC31518COV1001, VAC31518COV1002, VAC31518COV1003, VAC31518COV2001, VAC31518COV2004, VAC31518COV2008, VAC31518COV3001, VAC31518COV3003, VAC31518COV3005, VAC31518COV3006 and VAC31518COV3009.
The number of subjects exposed to study vaccine in blinded trials (Ad26 and placebo for Trial VAC31518COV3005, and placebo for Trial VAC31518COV3006) are estimates.
A total of 25,829 subjects (506 from Trial VAC31518COV1001, 150 from Trial VAC31518COV2001, 16,045 from Trial VAC31518COV3001, 781 from Trial VAC31518COV3005, 114 from Trial VAC31518COV3006, 8,233 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

Post-approval (non-clinical trial) 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 2022) for the United States (US), European Centre for Disease Prevention and Control (ECDC 2022) for European Economic Area (EEA) countries/territories, Korea Disease Control and Prevention Agency (KDCA 2022) for South Korea, Ministério da Saúde (Ministério da Saúde 2021) for Brazil, and National Department of Health (NDH 2022) for South Africa. The vaccine exposure figures described in this section are an overall estimation with some
uncertainties regarding the lack of exposure information received from many countries/territories.

Interval Exposure Estimates

The interval subject exposure for the Ad26.COV2.S vaccine during the reporting period (01 March 2022 to 31 August 2022) is provided in Table 8 below.

Table 8: Subject Exposure to the Ad26.COV2.S Vaccine During the Reporting Period (01 March 2022 to 31 August 2022)

Region/Country/Territory	Number of Distributed Doses[a]	Number of Administered Doses[b]
EEA		
Austria	0	5,326
Belgium	0	2,848
Bulgaria	0	18,340
Croatia	31,200	4,538
Cyprus	16,800	1,401
Czechia	55,200	1,890

Estonia	0	1,225
France	0	19,677
Germany	1,000,800	128,246
Greece	0	54,912
Hungary	369,600	10,300
Iceland	0	20
Italy	0	249
Latvia	0	1,852
Liechtenstein	NR	3
Lithuania	50,400	1,484
Luxembourg	0	36
Malta	0	116
Norway	0	313
Poland	0	161,697
Portugal	0	4,163
Romania	0	28,117
Slovakia	0	2,479
Spain	0	281
ROW		
Afghanistan	8,150,400	NR
Benin	885,600	NR
Brazil	500	NR
Burkina Faso	2,007,650	NR
Cameroon	2,340,000	NR
Chad	6,982,550	NR
Colombia	4,800	NR
Congo (Brazzaville)	1,177,400	NR
Congo (Kinshasa)	6,213,600	NR
Djibouti	158,400	NR
Ethiopia	14,817,600	NR
Gambia	192,000	NR
Guinea	172,800	NR
Guinea-Bissau	237,600	NR
Guyana	36,000	NR
Kenya	4,327,200	NR
Liberia	1,944,000	NR
Madagascar	1,718,400	NR
Malawi	1,987,200	NR
Mali	907,200	NR
Namibia	151,200	NR
Niger	561,600	NR
Nigeria	36,086,400	NR
Papua New Guinea	216,000	NR
Sierra Leone	1,776,000	NR
Solomon Islands	100,800	NR
South Africa	NR	84,146
South Korea	491,600	722
South Sudan	1,891,300	NR
Sudan	2,829,600	NR
Uganda	3,784,800	NR
Ukraine	100,800	NR
United Republic of Tanzania	13,372,250	NR
Vanuatu	14,400	NR
Yemen	237,600	NR
Zambia	5,219,950	NR
US	**5,963,100**	**436,117**
Total	**128,582,300**	**970,498**

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; NDH=National Department of Health; NR=Not Reported; ROW=Rest of World; US=United States

a: Number of vaccine doses distributed were reported from LYNX Finance.

b: Number of vaccine doses administered were reported from CDC for the US, from ECDC for EEA countries/territories, KDCA for South Korea, and NDH for South Africa. The data for administered doses for South Africa were available from 30 June 2022 to 31 August 2022.

Cumulative Exposure Estimates

The cumulative subject exposure for the Ad26.COV2.S vaccine from launch to 31 August 2022 is provided in Table 9 below.

Table 9: Cumulative Subject Exposure to the Ad26.COV2.S Vaccine From Launch to 31 August 2022

Region/Country/Territory	Number of Distributed Doses[a]	Number of Administered Doses[b]
EEA		
Austria	1,292,400	367,950
Belgium	629,200	427,716
Bulgaria	1,777,300	526,264
Croatia	309,550	204,108
Cyprus	142,500	30,944
Czechia	547,200	412,908
Denmark[c]	1,198,800	46,626
Estonia	110,800	78,932
Finland	68,400	NR
France	3,416,300	1,088,828
Germany	7,818,150	3,749,759
Greece	1,521,600	783,384
Hungary	4,309,200	341,801
Iceland[d]	33,500	54,303
Ireland[c]	281,500	237,097
Italy	2,370,000	1,482,636
Latvia	767,800	277,651
Liechtenstein	NR	264
Lithuania[d]	287,200	295,758
Luxembourg	80,200	41,521
Malta	116,400	32,398
Netherlands[c]	2,464,800	755,619
Norway	403,900	7,325
Poland	15,523,300	2,916,681
Portugal[d]	993,600	1,136,990
Romania	4,080,300	2,064,966
Slovakia	475,200	185,185
Slovenia[c]	230,400	135,989
Spain	2,659,000	1,980,822
Sweden	55,200	NR
ROW		
Afghanistan	14,695,250	NR
Algeria	6,285,600	NR
Angola	4,696,050	NR
Antigua and Barbuda	38,400	NR
Bahamas	38,400	NR
Bangladesh	679,750	NR
Belize	148,800	NR
Benin	3,566,400	NR
Bolivia	1,008,000	NR
Botswana	1,346,400	NR
Brazil	41,000,500	4,821,930
Burkina Faso	4,057,250	NR
Burundi	302,400	NR
Cambodia	1,060,100	NR
Cameroon	3,742,250	NR
Canada	168,000	NR
Central African Republic	2,016,300	NR
Chad	7,793,650	NR
Colombia	11,504,800	NR
Congo, (Brazzaville)	2,696,600	NR
Congo, (Kinshasa)	8,632,800	NR
Côte D'ivoire	5,272,600	NR
Djibouti	360,000	NR
Egypt	15,513,450	NR
Ethiopia	41,759,750	NR
Gabon	866,400	NR
Gambia	547,200	NR
Ghana	8,788,800	NR
Guinea	1,080,000	NR
Guinea-Bissau	1,368,000	NR
Guyana	96,000	NR
Haiti	165,600	NR
Jamaica	216,000	NR
Kenya	14,745,050	NR
Lao PDR	1,771,200	NR
Lebanon	336,000	NR

Lesotho	1,033,050	NR
Liberia	3,132,000	NR
Madagascar	3,537,950	NR
Malawi	3,568,350	NR
Mali	1,452,000	NR
Mauritania	2,282,400	NR
Mauritius	439,200	NR
Mexico	1,350,000	NR
Moldova	302,400	NR
Morocco	302,400	NR
Mozambique	8,989,700	NR
Namibia	650,400	NR
Nepal	3,711,500	NR
Nicaragua	993,600	NR
Niger	3,470,400	NR
Nigeria	49,002,850	NR
Papua New Guinea	820,800	NR
Philippines	12,725,650	NR
Rwanda	897,600	NR
Saint Lucia	7,200	NR
Sao Tome and Principe	100,800	NR
Senegal	1,739,100	NR
Sierra Leone	2,877,600	NR
Solomon Islands	100,800	NR
South Africa	19,623,200	7,805,749
South Korea	3,411,000	1,517,251
South Sudan	2,793,050	NR
Sudan	6,728,300	NR
Swaziland	302,400	NR
Switzerland	200	NR
Syrian Arab Republic (Syria)	3,458,400	NR
Togo	2,620,800	NR
Trinidad and Tobago	259,200	NR
Tunisia	1,540,800	NR
Turkey	832,800	NR
Uganda	15,820,800	NR
Ukraine	100,800	NR
United Republic of Tanzania	14,953,400	NR
Vanuatu	43,150	NR
Yemen	1,197,600	NR
Zambia	9,842,350	NR
US	41,225,650	18,875,222
Total	**490,569,100**[e]	**52,684,577**

Key: CDC=Centers for Disease Control and Prevention, ECDC=European Centre for Disease Prevention and Control, EEA=European Economic Area; EU=European Union; KDCA=Korea Disease Control and Prevention Agency; NDH=National Department of Health; NR=Not Reported; PDR=People's Democratic Republic; ROW=Rest of World; US=United States

a: Number of vaccine doses distributed were reported from LYNX Finance.

b: Number of vaccine doses administered were reported from CDC for the US, from ECDC for EEA countries/territories, from KDCA for South Korea, Ministério da Saúde for Brazil, and from NDH for South Africa. The data for administered doses for Brazil were last updated by the Ministério da Saúde website on 15 November 2021.

c: Information within the ECDC website states that, "*All data are subject to retrospective correction*" which may be a reason a decrease in the cumulative exposure has been observed for this country/territory. Exposure values were obtained from the most current counts as of 31 August 2022.

d: The number of distributed doses is less than the number of administered doses. This is the limitation when the data was distributed and reported. Some countries/territories may donate their surplus to other countries/territories resulting in this difference.

e: This count includes donated doses by the US and EU to various countries/territories, including donations through the GAVI/COVAX agreement.

Homologous Ad26.COV2.S Vaccine Booster Doses for Interval and Cumulative Period

The list of countries/territories along with number of homologous Ad26.COV2.S vaccine booster doses for the interval and cumulative period is provided in Table 10.

Table 10: Total Number of Subjects With the Homologous Ad26.COV2.S Vaccine Booster Doses

Country/Territory	Interval	Cumulative
South Africa	95,960	1,386,703
South Korea	407	26,986
US	138,125	1,566,109
Total	**234,492**	**2,979,798**

Key: US=United States

Exposure by Age for Ad26.COV2.S in EEA

Age stratifications based upon the number of administered doses available for EEA from the ECDC is unavailable as the data were last updated in September 2021. In addition, other stratifications such as sex, usage in pregnant or breastfeeding women, usage in hepatic impairment population, and usage in renal impairment population are also unavailable at this time.

Post-authorisation use in special populations

There is no available information on post-authorisation use of Ad26.COV2.S in special populations.

Other Post-approval Use

There is no available information on the pattern of use of Ad26.COV2.S which may be considered relevant for the interpretation of safety data.

Rapporteur assessment comment:

During the reporting period 1 March 2022 to 31 August 2022, a total of 128,582,300 doses of Ad26.COV2.S vaccine were estimated to have been distributed worldwide. Of these, approximately 1,524,000 doses were distributed the EEA countries, 5,963,100 to the US and the rest to the ROW-countries. In EU the largest number of administered doses was in Poland (161,697) and Germany (128,246). The distribution and administration of Ad26.COV2.S vaccine in EEA countries is clearly lower compared to previous reporting period (last PSUR described that approximately 30,000,000 doses was distributed in EEA countries).

A total of 490,569,100 doses of Ad26.COV2.S vaccine were estimated to have been distributed worldwide from launch to 31 August 2022. During the same period of time, a total of 52,684,577 doses of Ad26.COV2.S vaccine were estimated to have been administered worldwide. However, the numbers of administered doses have only been provided from EEA, Brazil, the US, South Africa and South Korea.

From launch to 31 August 2022, a total of 2,979,492 subjects were estimated to have been administered a homologous booster of Ad26.COV2.S vaccine in South Africa, South Korea and the US. A total of 234,492 subjects were estimated to have been administered a homologous booster of Ad26.COV2.S vaccine in South Africa, South Korea and the US during the reporting interval 1 March 2022 to 31 August 2022.

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-2022 to 24-Aug-2022).

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:

During the reporting period, 25,785 serious ARs and 42,477 non-serious ARs were received from spontaneous sources and 658 serious ARs were received from non-interventional post-marketing studies and other solicited sources. From spontaneous sources, non-interventional post-marketing studies, and other solicited sources, the SOCs including the most reported ARs were:
- General disorders and administration site conditions: 22,636
- Nervous system disorders: 10,227
- Musculoskeletal and connective tissue disorders: 7,178
- Infections and infestations: 6,574
- Gastrointestinal disorders: 3,259

Cumulatively, 92,932 serious ARs (91,813 spontaneous, 1,119 from non-interventional post-marketing studies and other solicited sources) were received by the MAH.

In this reporting period and in comparison, to previous PSUR, no new important safety information is identified.

1.3.5. Findings from clinical trials and other sources

1.3.5.1. Completed clinical trials

During the PBRER reporting period, one Company-sponsored interventional clinical trial (VAC31518COV2001) of Ad26.COV2.S was completed.

Trial VAC31518COV2001
Phase 2a, randomised, double-blind, placebo-controlled, multicentre trial evaluating Ad26.COV2.S across a range of dose levels and vaccination intervals in healthy adults aged 18 to 55 years inclusive, and adults in good or stable health aged 65 years and older to evaluate a single-dose level of Ad26.COV2.S (2.5×1010 vp) in healthy adolescents aged 16 to 17 years inclusive. In this trial, total 537 participants were exposed to Ad26.COV2.S of which 507 were adults and 30 were adolescents.

Rapporteur assessment comment:

During the reporting period, one phase 2 study was completed (VAC31518COV2001). This is not assessed in detail in this procedure. Overall, no new safety concern was detected.

1.3.5.2. Ongoing clinical trials

During the PBRER reporting period, 10 company-sponsored interventional clinical trials of Ad26.COV2.S (VAC31518COV1001, VAC31518COV1002, VAC31518COV1003, VAC31518COV2004, VAC31518COV2008, VAC31518COV3001, VAC31518COV3003, VAC31518COV3005, VAC31518COV3006, and VAC31518COV3009) were ongoing. No significant safety findings were identified from these trials during the reporting period.

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 for Ad26.COV2.S during the reporting period.

Other Therapeutic Use of Medicinal Product
During the reporting period, no pre-approval patient access programmes/registries supported by the Company are ongoing or completed for Ad26.COV2.S.

New Safety Data Related to Fixed Combination Therapies
This section is not applicable as there are no marketed combination therapies with Ad26.COV2.S.

Rapporteur assessment comment:

During the reporting period, 10 MAH sponsored clinical trials of Ad26.COV2.S were ongoing (VAC31518COV1001, VAC31518COV1002, VAC31518COV1003, VAC31518COV2004, VAC31518COV2008, VAC31518COV3001, VAC31518COV3003, VAC31518COV3005, VAC31518COV3006, and VAC31518COV3009). No new safety signal was identified during the reporting period.

Findings from non-interventional studies

The Company-sponsored (VAC31518COV4002 and VAC31518COV3021), collaborative, and publicly available real-world evidence (RWE) studies reporting on the vaccine effectiveness of Ad26.COV2.S are ongoing. Interim results are available for study VAC31518COV4002 which is an observational longitudinal post-authorisation study to assess the effectiveness of a single-dose of Ad26.COV2.S (5×10^{10} vp) in clinical practice, with onset 14 days after vaccination, in adults ≥18 years of age in the US. The RWE findings support and extend the conclusions of the pivotal efficacy trial. The protection against COVID-19 varies between different variants of concern. Single-dose Ad26.COV2.S VE against infection were reported to be lower during Omicron-emerging and Omicron-predominated periods. Fully vaccinated individuals who received a Ad26.COV2.S booster vaccine showed an increase in VE during the Omicron periods as reported in RWE studies.

Rapporteur assessment comment:

Available RWE are used by the MAH to study the vaccine effectiveness. The effectiveness has been dependent on the different circulating variants of SARS-CoV-2.. No new safety concern is detected here.

1.3.5.3. Other Clinical Trials

During the PBRER reporting period, 8 interventional clinical studies were ongoing: 1 interventional clinical study (COV-BOOST [VAC31518COV2009]) sponsored by the University Hospital Southampton NHS Foundation Trust, 1 interventional clinical study (VAC31518COV2012) sponsored by the Vaccine Trial Centre (Hospital for Tropical Diseases, Mahidol University, Thailand), 1 interventional clinical study (VAC31518COV2016 [AUR1-8-341]) sponsored by The Aurum Institute NPC, 2 interventional clinical studies (VAC31518COV3012 [Sisonke {Together}] and VAC31518COV3021 [Sisonke Boost Open-Label Study {SISONKE2}]) sponsored by SAMRC, 1 interventional clinical study (VAC31518COV3018) sponsored by the Mayo Clinic, 1 interventional clinical study (VAC31518COV4012) sponsored by the National and Kapodistrian University of Athens, University Research Institute of Maternal and Child Health & Precision Medicine and 1 interventional clinical study (DMID 21-0012) sponsored by NIH were ongoing for Ad26.COV2.S. Of these 8 studies, 3 (VAC31518COV2016, VAC31518COV3018, and VAC31518COV4012) were initiated during the reporting period.

During the reporting period, no relevant safety information related to Ad26.COV2.S from these clinical studies became available.

Rapporteur assessment comment:

During the reporting period 25 Feb 2022 to 24 Aug 2022, 8 interventional clinical studies were ongoing. No new safety signal was identified in these studies during this period.

1.3.5.4. Medication Errors

Cases of medication error or potential medication error are reviewed in all PBRERs. Medication error is synonymous with vaccination error.

Methods

The Company global safety database was searched for medically confirmed and medically unconfirmed cases, received during this reporting period and cumulatively, which coded to the MedDRA Standardised MedDRA Query (SMQ) Medication errors (broad).

Results/Discussion

Primary Dose

During the reporting period of 25 February2022 to 24 August2022, 172 (146 medically confirmed and 26 medically unconfirmed) initial, primary dose cases reporting medication errors were identified. Of these 172 cases, 9 were serious and 163 were nonserious and reported a total of 294 events (4 serious; 290 nonserious) of medication errors. Of these 172 initial, primary dose cases reported during the reporting period of 25 February 2022 to 24 August 2022, 1 was reported from a Janssen Sponsored Clinical Study and

171 were from post-marketing sources (including spontaneous and solicited cases). No cases were retrieved from Janssen Supported Clinical Studies. Of the 171 cases, 12 concerned paediatric patients. Of the remaining 159 cases, the age range was from 18 to 83 years and 148 cases were reported from US. The majority of the cases included the PT of Expired product administered, Poor quality product administered, and/or Product storage error, and reflected that either the vaccine was administered beyond the expiration date, or after incorrect storage (temperature excursion or vaccine being drawn from a punctured vial kept beyond the recommended storage time). The majority (86.2%; 137/159) of post-marketing initial, primary dose cases involved medication errors without any additional AEs reported (classified as error without harm); whereas 13.8% (22/159) of cases reported medication errors with harm. These 22 cases reported 85 additional AEs (34 serious; 51 nonserious). The most frequently reported events of medication errors in these cases (n≥2) were inappropriate schedule of product administration (n=10), and product administered at inappropriate site, product administered to patient of inappropriate age, and wrong technique in product usage process (n=2 each). The frequency distribution of additional AEs (n≥2) reported in 22 post-marketing, primary dose cases reporting medication errors with harm with the use of Ad26.COV2.S is presented in Table 13 below. Most of the AEs were nonserious and presented local and systemic reactogenicity to Ad26.COV2.S. There were no fatal post-marketing primary dose cases retrieved from the search of the Company global safety database during the interval reporting period of 25 February 2022 to 24 August 2022.

Table 13: Frequency Distribution of Additional AEs in Post-marketing, Primary Dose Cases Involving Use of Ad26.COV2.S and Reporting Medication Errors With Harm

Additional AEs	Number of Events Received During the Reporting Period[a,b]		Number of Events Received Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Fatigue	1	3	10	80
Chills	1	2	4	65
COVID-19	0	3	5	10
Headache	0	3	11	99
Limb discomfort	1	2	2	8
Pain in extremity	1	2	8	73
Arthralgia	1	1	4	30
Condition aggravated	1	1	2	2
Dizziness	1	1	6	29
Hyperhidrosis	1	1	5	15
Myalgia	0	2	4	36
Nausea	1	1	4	41
Pyrexia	0	2	7	88

Key: AE=Adverse Event; COVID-19=Coronavirus Disease-2019

a: A single case may report more than 1 additional AE. Additional AEs with frequency ≥2 have been presented.

b: Additional AEs were sorted by descending frequency for the reporting period (25 February 2022 to 24 August 2022).

Cumulatively, 2,489 (1,774 medically confirmed and 715 medically unconfirmed) primary dose cases reporting medication errors were identified. Of these cases, 174 cases were serious and 2,315 were nonserious and reported a total of 3,241 events (46 serious; 3,195 nonserious) of medication errors. Of the 2,489 cumulative primary dose cases received, 7 were reported from Janssen Sponsored Clinical Studies, 24 from Janssen Supported Clinical Studies, and 2,458 from post-marketing sources (including spontaneous and solicited cases).

Booster Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 339 (82 medically confirmed and 257 medically unconfirmed) initial cases reported as booster were identified. There were 45 serious and 294 nonserious cases and reported a total of 348 events (10 serious; 338 nonserious) of medication errors. Of these cases, 187 were heterologous and 152 were homologous.

Of these 339 initial cases reported as booster during the interval, 2 were reported from Janssen Sponsored Clinical Studies (none of them related to vaccination-one insulin pump malfunction and one unspecific drug overdose) and 337 from post-marketing sources (including spontaneous and solicited). No cases were retrieved from Janssen Supported Clinical Studies. Of the remaining 337 cases, 5 concerned paediatric patients. The remaining 332 booster dose cases reported 340 events (8 serious; 332 nonserious) of

medication errors. The age range was 18-91 years, and the majority (n=237) of the cases were reported from Brazil followed by US (n=33).

Cumulatively, 1,071 (279 medically confirmed and 792 medically unconfirmed) cases reported as booster were identified. Of these cases, 83 cases were serious and 988 were nonserious and reported a total of 1,112 events (17 serious; 1,095 nonserious) of medication errors. Of these cases, 688 were homologous and 383 were heterologous. Of the 1,071 cumulative cases reported as booster, 2 were reported from Janssen Sponsored Clinical Studies and 1,069 from post-marketing sources (including spontaneous and solicited cases). No cases were retrieved from Janssen Supported Clinical Studies.

The frequency distribution of the MedDRA PTs of interest reported in post-marketing cases reported as booster is presented in Table 15 below. A single case may contain more than 1 EOI.

Table 15: Frequency of MedDRA PTs of Interest in Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Medication Errors

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Inappropriate schedule of product administration	0	311	0	877
Interchange of vaccine products	6	3	12	8
Product storage error	0	5	0	13
Poor quality product administered	0	4	0	19
Underdose	1	2	1	73
Incorrect route of product administration	0	2	0	5
Wrong product administered	1	1	1	3
Wrong technique in product usage process	0	2	0	4
Extra dose administered	0	1	0	3
Product use issue	0	1	0	1

Key: MedDRA=Medical Dictionary for Regulatory Activities; n=Number; PT=Preferred Term
a: The MedDRA PTs of interest are sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event of interest.

Of the 332 cases reported as booster, the majority (84.03%; 279/332) of them contained additional AEs (classified as medication errors with harm). The frequency distribution of additional AEs (n≥10) reported in these cases is presented in Table 16 below. The most frequently reported events were nonserious and represented local and systemic reactogenicity to Ad26.COV2.S. and adverse reactions of hypersensitivity.

Table 16: Frequency Distribution of Additional AEs in Post-marketing Cases Reported as Booster Involving Use of Ad26.COV2.S and Reporting Medication Errors With Harm

Additional AEs	Number of Events Received During the Reporting Period[a,b]		Number of Events Received Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Pyrexia	0	95	0	200
Headache	1	78	2	170
Pain	1	68	1	127
Pain in extremity	0	37	3	67
Chills	0	35	0	100
Fatigue	0	34	0	110
Malaise	1	27	2	48
Asthenia	0	26	1	41
Injection site pain	0	24	0	67
Feeling abnormal	0	22	1	35
Dizziness	0	21	0	57
Arthralgia	1	19	2	49
Vaccination site pain	0	20	0	39
Dyspnoea	0	17	2	44
Nausea	0	17	2	57
Paraesthesia	0	16	1	29
Myalgia	0	14	0	103
COVID-19	3	9	6	21
Pruritus	1	11	1	24
Tremor	0	12	0	15
Erythema	0	11	1	18
Hypersensitivity	0	11	0	16
Peripheral swelling	0	11	1	12
Application site pain	0	10	0	18
Illness	0	10	0	13
Rash	1	9	2	14
Swelling	0	10	0	12

Key: AE=Adverse Event; COVID-19=Coronavirus Disease-2019
a: A single case may report more than 1 additional AEs. Additional AEs with frequency ≥10 have been presented.
b: Additional AEs were sorted by descending frequency for the reporting period (25 February 2022 to 24 August 2022).

During the reporting period of 25 February 2022 to 24 August 2022, 3 fatal cases reported as booster were retrieved, referring to a 60-year-old patient and 2 patients with unknown age. Reported causes of death were myocardial infarction (n=1), an unspecified adverse event (n=1) and thrombosis, haemorrhage and myocardial infarction (n=1), this case is also included in the analysis of cases with Coronary Artery Disease. All 3 cases lacked information for an adequate medical assessment, including medical history, latency, nature and/or clinical course of the reported fatal AEs.

Paediatric cases

Primary dose

During the reporting period of 25 February 2022 to 24 August 2022, 12 (9 medically confirmed and 3 medically unconfirmed) post-marketing sources (including spontaneous and solicited), initial, primary dose cases reporting medication errors in paediatric population were retrieved. These 12 post-marketing, initial, primary dose cases reported 15 events (1 serious; 14 nonserious) of medication errors. Most of the cases occurred in subjects aged 12-17 years (n=11), and five of the cases were reported from US followed by Canada and South Africa (n=2, each).

Cumulatively, 371 (193 medically confirmed and 178 medically unconfirmed) post-marketing, primary dose cases reporting medication errors in paediatric population were identified. Of these cases, 23 cases were serious and 348 were nonserious and reported a total of 400 events (7 serious; 393 nonserious) of medication errors.

Table 18: Frequency of MedDRA PTs of Interest in Post-marketing, Primary Dose Cases Reporting Medication Errors in Paediatric Population With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Product administered to patient of inappropriate age	0	11	3	341
Circumstance or information capable of leading to medication error	1	0	1	0
Incorrect dose administered	0	1	0	1
Poor quality product administered	0	1	0	4
Product use issue	0	1	0	20

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

a: The MedDRA PTs of interest are sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event of interest.

More than half (66.7%; 8/12) of the post-marketing initial, primary dose paediatric cases involved medication errors without harm, ie, no additional AEs were reported. In the remaining 4 out of the 12 cases, 20 additional AEs (all nonserious) were reported. The frequency distribution of additional AEs reported in post-marketing, primary dose cases reporting medication errors with harm in paediatric population with the use of Ad26.COV2.S represented local or systemic reactogenicity to Ad26.COV2.S. There were no fatal post-marketing primary dose cases.

Table 19: Frequency Distribution of Additional AEs in Primary Dose Cases Involving Use of Ad26.COV2.S and Reporting Medication Errors in Paediatric Population

Additional AEs	Number of Events Received During the Reporting Period[a,b]		Number of Events Received Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Pyrexia	0	3	2	44
Pain	0	2	1	7
Bedridden	0	1	0	1
Chest pain	0	1	0	1
Chills	0	1	1	14
COVID-19	0	1	0	3
Erythema	0	1	0	1
Fatigue	0	1	0	12
Headache	0	1	0	40
Illness	0	1	0	2
Lymphadenitis	0	1	0	1
Malaise	0	1	1	8
Musculoskeletal disorder	0	1	0	1
Nasopharyngitis	0	1	0	1
Nausea	0	1	0	7
Pruritus	0	1	0	1
Swelling	0	1	0	2

Key: AE=Adverse Event; COVID-19=Coronavirus Disease-2019
a: A single case may report more than 1 additional AE.
b: Additional AEs were sorted by descending frequency for the reporting period (25 February 2022 to 24 August 2022).

Booster dose

During the reporting period of 5 February 2022 to 24 August 2022, 5 post-marketing sources (including spontaneous and solicited), initial cases reported as booster which reported medication errors in paediatric population were retrieved. These 5 post-marketing, initial, booster dose cases reported 6 events (no serious; 6 nonserious) of medication errors. All of them occurred in subjects aged 13-17 years, four cases were reported from Brazil and one from Canada. Of the 5 post-marketing, initial cases reported as booster in paediatric population retrieved during the reporting period, the majority (80%; 4/5) reported the PT of Off label use (all of them nonserious) and the majority (80%, 4/5) of the cases reported additional AEs. No fatal cases were reported.

Cumulatively, 7 (4 medically confirmed and 3 medically unconfirmed) post-marketing cases reported as booster which reported medication errors in paediatric population were identified. Of these cases, 1 was serious and 6 were nonserious and reported a total of 10 events (no serious; 10 nonserious) of medication errors.

The frequency distribution of additional AEs reported in these 5 cases is presented in Table 22 below. All serious events were reported in 1 medically unconfirmed case, which concerned a 13-year-old male with underlying autism and multiple allergies, who was also on concomitant medications of risperidone and amitriptyline. The patient was administered a primary dose of tozinameran and within 2 to 6 weeks took an Ad26.COV2.S booster dose instead of tozinameran by mistake. The patient was hospitalised within 24 hours post-booster dose and was reported to have cardiac ischaemia and renal failure (medically unconfirmed). In the absence of a clear diagnosis, and the presence of confounding medications (antipsychotics, which can have similar effects), an adequate causality assessment could not be performed.

Table 22: Frequency Distribution of Additional AEs in Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Medication Errors With Harm in Paediatric Population

Additional AEs	Number of Events Received During the Reporting Period[a,b]		Number of Events Received Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Headache	0	2	0	2
Abdominal pain upper	1	0	1	0
Application site discolouration	0	1	0	1
Arrhythmia	1	0	1	0
Axillary mass	0	1	0	1
Depressed mood	0	1	0	1
Fatigue	0	1	0	1
Muscle spasms	1	0	1	0
Myocardial ischaemia	1	0	1	0
Nausea	1	0	1	0
Pyrexia	1	0	1	0
Renal failure	1	0	1	0
Vomiting	1	0	1	0

Key: AE=Adverse Event; COVID-19=Coronavirus Disease-2019

a: A single case may report more than 1 Additional AEs.

b: Additional AEs of interest were sorted by descending frequency for the reporting period (25 February 2022 to 24 August 2022).

Rapporteur assessment comment:

Evaluation of the data on medication errors received for Ad26.COV2.S during the reporting period did not identify patterns of medication errors and/or potential medication errors suggestive for a new safety concern.

Cases of product use in a limited number of children have been reported, most of them in the age range 12-17 years and reported from US (primary dose) and Brazil (booster dose). No new safety issues were identified through review of these paediatric cases.

1.3.5.5. Non-clinical data

During the period covered by this report, no new non-clinical trial safety concerns were identified for Ad26.COV2.S

1.3.5.6. Literature

The MAH periodically conducts comprehensive searches of the scientific databases MEDLINE® and Embase®, which also includes abstracts presented at scientific meetings, to identify safety and/or efficacy information that may affect or further inform the benefit-risk profile the Ad26.COV2.S. It should be noted that the literature searches are wider than those for individual case safety reports and include studies reporting safety outcomes in groups of subjects. The search also includes information relevant to other similar vaccines and vaccine components such as stabilisers, preservatives and adjuvants. In addition, if the MAH becomes aware of new safety/efficacy information from unpublished abstracts/manuscripts these would also be considered for evaluation and the findings will be discussed.

Selected references and Sponsor Comments are presented below.

Product specific literature:

Anastassopoulou C, Hatziantoniou S, Vlachopoulos C, et al. Temporal relationship of myocarditis and pericarditis following COVID-19 vaccination: A pragmatic approach. Int. J.

Cardiol. 2022.

Background: Complications following COVID-19 vaccination, particularly with mRNA vaccines, rarely include myocarditis and pericarditis. This work principally aimed at defining a realistic temporal relationship between vaccination and myocarditis/pericarditis development.

Method: All relevant cases reported from week 52/2020 through week 41/2021 in the VAERS database were retrieved and analysed for licensed vaccines. These included BNT162b2, mRNA-1273, and AD26.COV2.S. Incidence rates were calculated using the corresponding administered vaccine doses as denominators. Additionally, analysed parameters included demographics, dose series, hospitalisation length, and outcome.

Results: Overall, 2,016 myocarditis and 1,380 pericarditis cases, (4.96/106 and 3.40/106 administered vaccine doses, respectively), were recorded. Most myocarditis cases occurred following BNT162b2 (5.60/106 doses) in males <30 years. Pericarditis affected predominantly males <40, both sexes >40 years, and was most common post AD26.COV2.S (4.78/106 doses). Hospitalisation was required for 40.3% and 27.2% of myocarditis and pericarditis cases, respectively. A bimodal pattern was found for both myocarditis and pericarditis, with 2 peaks that coincided temporally, but were reversed in intensity. The first peak was recorded 1 to 3 days post-vaccination and was more pronounced in myocarditis, while the second was recorded 15 to 30 days post-vaccination and was more intense in pericarditis. Conclusion: Myocarditis/pericarditis after COVID-19 vaccination is rare and depicts a bimodal pattern.

MAH Comments: As summarised by the authors, "Most myocarditis cases occurred following BNT162b2 (5.60/106 doses) in males <30 years. Pericarditis affected predominantly males <40, both sexes >40years, and was most common post AD26.COV2.S (4.78/106 doses)." Myocarditis and pericarditis have been closely monitored by the Company. Based on the cumulative review of the totality of the Ad26.COV2 data, the Company considered that the available data was insufficient to establish a causal association between Ad26.COV2.S and myocarditis/pericarditis. The Company will continue to closely monitor cardiac inflammatory disorders as an AESI. No new safety signal was identified.

Rapporteur assessment comment:
In this publication, pericarditis was reported after $4.78/10^6$ doses of AD26.COV2.S. The MAH should continue to closely monitor cardiac inflammatory disorders as an AESI.

Frontera JA, Tamborska AA, Doheim MF, et al. Neurological Events Reported after COVID-19 Vaccines: An Analysis of VAERS. Ann. Neurol. 2022.

Objective: To identify the rates of neurological events following administration of mRNA (Pfizer, Moderna) or adenovirus vector (Janssen) vaccines in the US.

Methods: We utilised publicly available data from the US VAERS collected between 01 January 2021 to 01 June 2021. All free text symptoms that were reported within 42 days of vaccine administration were manually reviewed and grouped into 36 individual neurological diagnostic categories. Post-vaccination neurological event rates were compared between vaccine types and to age-matched baseline incidence rates in the US and rates of neurological events following COVID-19.

Results: Of 306,907,697 COVID-19 vaccine doses administered during the study timeframe, 314,610 (0.1%) people reported any AE and 105,214 (0.03%) reported neurological AEs in a median of 1 day (IQR0 to 3) from inoculation. GBS, and cerebral venous thrombosis (CVT) occurred in fewer than 1 per 1,000,000 doses. Significantly more neurological AEs were reported following Janssen (Ad26.COV2.S) vaccination compared to either Pfizer-BioNtech (BNT162b2) or Moderna (mRNA-1273; 0.15% versus 0.03% versus 0.03% of doses, respectively P<0.0001). The observed-to-expected (O/E) ratios for GBS, CVT, and seizure following Janssen vaccination were >=1.5-fold higher than background rates. However, the rate of neurological events after acute SARS-CoV-2 infection was up to 617-fold higher than after COVID-19 vaccination.

Conclusion: Reports of serious neurological events following COVID-19 vaccination are rare. GBS, CVT, and seizure

may occur at higher than background rates following Janssen vaccination. Despite this, rates of neurological complications following acute SARS-CoV-2 infection are up to 617-fold higher than after COVID-19 vaccination.
MAH Comments: GBS, transverse myelitis, and thrombosis in combination with thrombocytopenia are known risks described in Section 4.4 (special warning and precaution) and Section 4.8 (undesirable effects) of the Summary of Product Characteristics (SmPC) for Ad26.COV2.S vaccine (Janssen COVID-19 vaccine SmPC 2021). Regarding seizures, the authors state that their findings "are considered exploratory, however, since syncope or convulsive syncope may be confused with seizure. Without access to the source medical records, we cannot infer causality;" Regarding the presented acute disseminated encephalomyelitis and meningoencephalitis (ADEM) data, the authors importantly point out "the wide confidence intervals (which cross 1.0)" No new safety information is detected at this time.

Rapporteur assessment comment:

GBS, transverse myelitis, and thrombosis in combination with thrombocytopenia are already included in the product information. No new safety concern is detected here.

Kyungu FM, Katumba AM, Kamwira HL, et al. Acute acalculous cholecystitis following COVID-19 vaccination: a case report. Pan Afr. Med. J. 2022; 41:291.

Abstract: Acute acalculous cholecystitis is an acute inflammation of the gallbladder in the absence of stones, usually occurring in elderly and critically ill patients with underlying conditions. A 29-year-old man presented to the hospital complaining of abdominal pain in the right hypochondrium with permanent fever, 3 days after Janssen COVID-19 vaccine inoculation. Abdominal ultrasound revealed a thickened gallbladder wall without evidence of gallstone consistent of an acute acalculous cholecystitis. Blood analyses revealed thrombocytopenia, eosinophilia and liver dysfunction. The
Polymerase Chain Reaction (PCR) COVID-19 test was negative. As treatment, the patient benefited of pain management, antibiotic, and fluid. In the evolution, there was a regression of clinical signs with persistence of liver dysfunction. The patient was discharged 10 days after hospitalisation. The Janssen COVID-19 vaccine is likely to induce acute acalculous cholecystitis as AE following vaccination.
MAH Comment: "Acalculous cholecystitis is an acute necroinflammatory disease of the gallbladder with a multifactorial pathogenesis. It accounts for approximately 10 percent of all cases of acute cholecystitis and is associated with high morbidity and mortality rates. [...] Pathologically in patients with acalculous cholecystitis, endothelial injury, gallbladder ischemia, and stasis, lead to concentration of bile salts, gallbladder distension, and eventually necrosis of the gallbladder tissue."16 According to the published literature17, some cases of acalculous cholecystitis have been reported after COVID-19 infection. The current case reported a "previously healthy" young man "without underlying medical conditions" who experienced the symptoms 3 days after vaccination. Although ultrasound examination revealed thickened gall bladder measuring approximately 7.7 mm without evidence of gallstones, as well as laboratory results revealed thrombocytopenia, eosinophilia, and liver dysfunction; however, an association to vaccination cannot be ascertained in this case. It was missing some data on full work-up for infections and differential diagnosis. No new safety signal is identified at this time.

Rapporteur assessment comment:

This short case-report describes a 29-year-old man who was diagnosed with acute acalculous cholecystitis 3 days after vaccination with Janssen Vaccine Covid-19, and the authors propose an association between vaccination and acalculous cholecystitis. The incomplete clinical information of this case limits the possibility of assessment of potential causal association.

Lareb.nl. Decreased milk supply during breastfeeding after COVID-19 vaccination. 2022. No abstract available.

MAH Comment: "In 2021, Lareb received nearly 200 reports from women who had noticed [temporarily less breast milk]. In most cases, the amount of breast milk returned to normal after a few days. " About 10% of the women said they had stopped breastfeeding. The fact that they have stopped does not necessarily have to be because they have received the corona vaccine". Out of 200 reports mentioned in the article, just 3 patients received Janssen vaccine, and most cases were reported following Pfizer vaccine (about 177)."Based on the reports of decreased milk supply during breastfeeding after COVID-19 vaccination, a causal relationship cannot be ruled out and should be further investigated. This potential adverse reaction may create a substantial burden for lactating women. More knowledge is important for informing lactating women." Use during pregnancy and while breastfeeding is classified as Missing Information in the core RMP (cRMP) for the Janssen COVID-19 vaccine, both a pregnancy registry (VAC31518COV4005) and an open-label phase 2 study in pregnant patients (VAC31518COV2004) are included in the PP. As also stated in the cRMP, "Breastfeeding women were excluded from all clinical trials, except from Phase 3 trials COV3001 and COV3009. Up to the DLP of the EU-RMP that was part of the initial cMAA submission (22 January 2021), 128 breastfeeding women have received Ad26.COV2.S in trial COV3001, but no data are currently available from these trials in this subpopulation. A small subset of participants within trial COV2004 will be followed up during breastfeeding to assess the transfer of antibodies via breast milk. the safety profile of Ad26.COV2.S in breastfeeding women has not been established and the risk in this population has not yet been defined." The Pregnancy, Breastfeeding, and Fertility Section of the CCDS states, "Safety data with TRADENAME when administered within 3 months before pregnancy as well as during pregnancy have shown no safety concerns in the mother or child in over 500 reported pregnancies, with over 100 reported pregnancy outcomes"

Rapporteur assessment comment:

In this report from "bijwerkingen centrum lareb" in NL, summarize data regarding women who reported temporarily less breast milk after covid-19 vaccination. The Authors mention that several factors may contribute to a decrease in milk supply, including maternal stress, obesity, preeclampsia, hypertension, diabetes and certain medications, limiting the possibility to draw conclusions regarding association with vaccination. Only 3 cases were reported among breast-feeding women to which Janssen covid-19 vaccine was administered. No new safety concern is detected here.

Merino D, Gerard AO, Van Obberghen EK, et al. COVID-19 Vaccine-Associated Transient Global Amnesia: A Disproportionality Analysis of the WHO Safety Database. Front. Pharmacol. 2022;13.

Abstract: COVID-19 spread rapidly, resulting in a global pandemic for which vaccines were quickly developed. As their safety continues to be monitored, cases of transient global amnesia (TGA) following mRNA vaccination with elasomeran have been reported. TGA is characterised by sudden onset of anterograde amnesia with preservation of other cognitive functions and resolution within 24 hours. We aimed to investigate the potential link of TGA with COVID-19 vaccines. We queried the WHO VigiBase for all reports of "Transient global amnesia", up to 06 December 2021. Disproportionality analysis relied on the Reporting Odds Ratio (ROR) with its 95% Confidence Interval (CI) and the Information Component (IC). A positive lower end of the 95% CI of the IC (IC025) is used to statistically detect a signal. Of all TGA cases, 289 were associated with a COVID-19 vaccine, representing the most frequent association. Tozinameran was mostly represented (147, 50.8%), followed by AZD1222 (69, 23.8%), elasomeran (60, 20.8%), and JNJ-78436735 (12, 4.2%). With an IC025 > 0, COVID-19 vaccines showed a significant ROR (5.1; 95%CI 4.4 to 6.0). Tozinameran reached the strongest ROR (4.6; 95%CI 3.9 to 5.0), followed by elasomeran (4.4; 95%CI 3.4 to 6.0), AZD1222 (3.8; 95%CI 3.0 to 5.0), and JNJ-78436735 (3.7; 95%CI 2.1 to 6.0). Our analysis of COVID-19 vaccines-related TGA reports shows significant

disproportionality. Cerebrovascular, inflammatory, or migrainous mechanisms may underlie this association. Yet, numerous confounding factors cannot be tackled with this approach, and causality cannot be ascertained. The identification of this trigger of TGA may help the clinician in his etiological research.
MAH Comment: Review of WHO safety database (Vigibase) of all notified TGA cases for the period from 14 November 1967 to 06 December 2021 was conducted. A disproportionality analysis identified that of all TGA cases, COVID-19 vaccine represented the most frequent association. Twelve reports for Janssen vaccine (4.2%) were identified. According to disproportionality analysis, COVID-19 vaccines were characterised by the strongest ROR with the strongest ROR reported for the Pfizer vaccine (ROR 4.6; 95% CI 3.9 to 5.0), followed by Moderna (ROR 4.4; 95% CI 3.4 to 6.0), AstraZeneca (ROR 3.8; 95% CI 3.0 to 5.0) and Janssen vaccine (ROR 3.7; 95% CI 2.1 to 6.0). No detailed information on TGA cases at the individual level was available; hence, given the study limitations (reporting bias, under-reporting, coding heterogeneity, incomplete data) an association to vaccination cannot be ascertained. Taking into consideration other potential aetiologic factors and missing information on these reports, no safety signal was identified at this time.

Rapporteur assessment comment:

This report concerns cases of TGA and vaccination against covid-19. Since the report does not include detailed information on the cases, it can be agreed with the MAH that it is not possible to draw any conclusions to Janssen covid-19 vaccine (n=12).

Moro P, Olson C, Clark E, et al. Post-authorization surveillance of adverse events following COVID-19 vaccines in pregnant persons in the vaccine adverse event reporting system (VAERS), December 2020 to October 2021. Vaccine. 2022;40(24):3389-3394.

Background: Pregnant persons are at increased risk of severe illness from COVID-19 infection, including intensive care unit admission, mechanical ventilation, and death compared with non-pregnant persons of reproductive age. Limited data are available on the safety of COVID-19 vaccines administered during and around the time of pregnancy.
Objective: To evaluate and summarise reports to the VAERS, a national spontaneous reporting system, in pregnant persons who received a COVID-19 vaccine to assess for potential vaccine safety problems. Method: We searched VAERS for US reports of AEs in pregnant persons who received a COVID-19 vaccine from 14 December 2020 to 31 October 2021. Clinicians reviewed reports and available medical records. Crude reporting rates for selected AEs were calculated, and disproportional reporting was assessed using data mining methods.
Results: VAERS received 3,462 reports of AEs in pregnant persons who received a COVID-19 vaccine; 1,831 (52.9%) after BNT162b2, 1,350 (38.9%) after mRNA-1273, and 275 (7.9%) after Ad26.COV2.S. Eight maternal deaths and 12 neonatal deaths were reported. Six-hundred twenty-one (17.9%) reports were serious. Pregnancy-specific outcomes included: 878 spontaneous abortions (<20 weeks), 101 episodes of vaginal bleeding, 76 preterm deliveries (<37 weeks), 62 stillbirths (≥20 weeks), and 33 outcomes with birth defects. Crude reporting rates for preterm deliveries and stillbirths, as well as maternal and neonatal mortality rates were below background rates from published sources. No disproportional reporting for any AE was observed.
Conclusion: Review of reports to VAERS following COVID-19 vaccines in pregnant persons did not identify any concerning patterns of maternal or infant-foetal outcomes.
MAH Comment: No new safety signal was identified. Use during pregnancy is classified as Missing Information in the RMP for the Janssen COVID-19 vaccine, both a pregnancy registry (VAC31518COV4005) and an open-label phase 2 study in pregnant patients (VAC31518COV2004) are included in the EU RMP and Pharmacovigilance Plan (PVP).

Rapporteur assessment comment:

This US study aimed to evaluate and summarise reports to the VAERS in pregnant person. No concerning patterns of maternal or infant-foetal outcome was identified.

Nyankerh CNA, Boateng AK, Appah M. Ocular Complications after COVID-19 Vaccination, Vaccine Adverse Event Reporting System. Vaccines. 2022;10(6).

Abstract: In December 2020, the US FDA licensed COVID-19 vaccines for emergency use authorisation. We investigated the ocular AE reports in patients reported to the VAERS following vaccination against COVID-19. We searched the VAERS database for US reports among persons who received COVID-19 vaccines between December 2020 and December 2021. Our goal was to analyse and quantify the ocular AEs submitted to VAERS to provide clinicians and researchers with a broader view of these ocular side effects. During the analysis period, VAERS received 55,313 AE reports and, after data cleaning, 6,688 reports met the inclusion criteria. Note that 2,229 (33.33%) AEs were classified as cases of eyelid swelling, ocular hyperemia, and conjunctivitis; 1,785 (26.69%) as blurred vision, and 1,322 (19.77%) as visual impairment. Females accounted for 73.8% of AE reports and the age group between 40 and 59 years had the most frequent AEs. A higher proportion of these AEs reported to VAERS was linked with the Janssen and Moderna COVID-19 vaccines. At the time of vaccination, a high proportion of patients reported conditions like allergies, hypertension, diabetes, thyroid disease, vascular, and other autoimmune diseases. A review of these data suggests a possible association between COVID-19 vaccines and ocular AEs. Physicians are cautioned not only to be aware of this potential problem, but to check any underlying patient conditions, and to carefully document in VAERS within a few weeks of vaccination. Future COVID-19 vaccine safety studies in healthy subjects would help clarify the vaccine's safety profile.

MAH Comment: The study aimed to "analyze and quantify the ocular adverse events submitted to VAERS to provide clinicians and researchers with a broader view of these ocular side effects." The period covered was December 2020 to December 2021. Out of the patients who had ocular complications, "3346 (50%) received the Pfizer-BioNTech vaccine, 2552 (38.2%) received the Moderna vaccine and 790 (11.8%) received the Janssen vaccine." According to the study authors, "To test the null hypothesis that the vaccines administered were associated with ocular adverse events, [they] performed a chi-square test of association. Surprisingly, the Janssen and Moderna vaccines were mostly associated with the reported ocular adverse events in VAERS." The authors stated that, "[...] the Janssen vaccine had a significantly higher proportion of adverse events for all cases except for eyelid swelling, ocular hyperemia, conjunctivitis, which had a higher proportion of adverse events associated with the Moderna vaccine." Worth mentioning that, "These ocular events have also been reported in patients who have suffered the COVID-19 disease, which may suggest a shared common pathway of the ocular complications associated with the COVID-19 disease and post-vaccination events." Nevertheless, the authors also emphasised that "since [they] did not have data showing the number of doses or boosters per vaccine type administered to each patient, trying to establish a cause-effect relationship will be implausible. Also, since VAERS does not include an unvaccinated group, [they] could not calculate rates nor determine if the vaccines themselves are associated with an increased risk of adverse events." Taking into consideration the study limitations (passive, biased, and stimulated reporting, missing information on cases, affected quality and accuracy of the information, etc), there is no new safety signal identified at this time.

Rapporteur assessment comment:

In this paper, ocular AE reports was searched in VAERS data base from dec 2020-dec 2021. No unvaccinated control group was included. No new safety concern is detected here.

Priluck A, Arevalo J, Pandit R. Ischemic retinal events after COVID-19 vaccination. Am. J. Ophthalmol. Case Rep. 2022;26.

Purpose: We report 2 cases of ischaemic retinal events occurring soon after administration of the Moderna and Johnson & Johnson/Janssen COVID-19 vaccines. To our knowledge, these are the first reports of isolated ischaemic retinal events occurring after COVID-19 vaccination.

Observations: A 57-year-old female had new onset floaters of the left eye within days of her second Moderna COVID-19 vaccination, which progressively worsened prompting her to present for evaluation. The patient was diagnosed with

a branch retinal vein occlusion in the left eye. A 20-year-old female presented with persistent central scotomata in both eyes, which she first noticed 2 days after her Johnson & Johnson/Jannsen COVID-19 vaccination. She was diagnosed with acute macular neuroretinopathy of both eyes.

Conclusion: The potential side effects of COVID-19 vaccines are still being established; however, there has been concern over pro-thrombotic events with these vaccines, with most concerns directed toward the Johnson & Johnson vaccine. We observed likely transient pro-thrombotic retinal milieu in patients who received these vaccines though it remains unclear whether there is a shared mechanism between systemic response to the COVID-19 spike protein and the highly pro-thrombotic state seen in COVID-19 infections. In the case of our patients, we postulate their immunologic responses to the vaccines and possibly a resultant pro-thrombotic state may have precipitated their ischaemic retinal events. We thus recommend that patients with ocular symptoms after COVID-19 vaccination undergo comprehensive ophthalmologic evaluation.

MAH Comment: Acute macular neuroretinopathy presents predominantly in females in their twenties, is bilateral in over half of patients, and while the mechanism(s) are poorly understood, has been associated with multiple potential risk factors, including in 1 series with oral contraceptives in 35.6% of patients (Bhavsar KV 2016). Both cases present acute macular neuroretinopathy after receiving COVID-19 vaccination: in the first case after the second dose of Moderna and in the second case after the Janssen COVID-19 vaccine. In the second case, the patient reported using norgestimate-ethinyl estradiol, which is an oral contraceptive. Use of oral contraceptives is a known risk factor for the development of acute macular neuroretinopathy (Bhavsar KV 2016). According to the PBRER covering the period of 25 August 2021 to 24 February 2022, "As requested in EMEA/H/C/005737/MEA/014.7: "[...] a cumulative review of acute macular
neuroretinopathy(AMN) in subjects having been vaccinated with the COVID-19 vaccine Janssen" was conducted. Based on the MAH conclusion, "A causal relationship between AMN and Ad26.COV2.S could not be established based on the totality of data analyzed including a cumulative review of cases reported in association with Ad26.COV2.S vaccine, the literature, and the O/E analysis. The Company will continue to monitor this event through routine pharmacovigilance activities." Based on the presented cases and both the known and unknown characteristics of this disease state, no new safety information is detected at this time.

Rapporteur assessment comment:

This case report concerns two cases of ischaemic retinal events, one of them in a 20-year-old female that 2 days after vaccination with Jansen Covid-19 vaccine was reported with persistent central scotoma (blind spot) and was diagnosed with acute macular neuroretinopathy of both eyes. A cumulative review of acute macular neuroretinopathy was requested in EMEA/H/C/005737/MEA/014.7, at that stage a causal relationship could not be established.

Rodriguez Quejada L, Toro Wills MF, Martinez-Avila MC, Patino-Aldana AF. Menstrual cycle disturbances after COVID-19 vaccination. Womens health. 2022;18: 17455057221109375. Introduction: After COVID-19 vaccination, women of reproductive age reported changes in their
menstrual cycle.

Materials and Methods: A retrospective study was carried out after a survey on social networks that included women aged 18 to 41 years with normal cycles according to International Federation of Gynaecology and Obstetrics and who were vaccinated (complete schedule for 2 doses, except J&J/Janssen or incomplete with a single dose). Women with the following conditions were excluded: pregnant or lactating women; history of diseases that cause menstrual irregularities or early menopause: anorexia, bulimia, polycystic ovary syndrome, hypothyroidism, obesity, or low weight; hysterectomised or oophorectomized patients; and high-performance athletes.

Results: Overall, 950 women completed the survey between July and September 2021. In total, 408 women met the inclusion criteria, and 184 reported the following characteristics: frequency (normal 43.47%, infrequent 25%, and

frequent 31.53%), regularity (regular 51.08%, irregular 42.93%, and absent/amenorrhoea 5.97%), duration (normal 65.21%, prolonged 26.08%, absent/amenorrhoea 8.69%), and volume (heavy 41.84%, light 20.65%, and absent/amenorrhoea 6.52%).

Conclusions: SARS-CoV-2 infection and COVID-19 vaccination can influence the menstrual cycle and cause alterations.

MAH Comment: The retrospective study results based on a survey of a women population aged 18 to 41 years identified per inclusion/exclusion criteria revealed that 184 women reported alterations in the menstrual cycle. "Of the 184 women who reported alterations in the menstrual cycle, [....] Overall, 150 (81.5%) women had a complete vaccination schedule, mostly with Sinovac (n=53; Pfizer (n=51), J&J/Janssen (n=33), others (n=19), Modern (n=15), AstraZeneca (n=13))." Janssen vaccine was identified as the one with more women in the subgroup who reported irregular cycles (n=19) than normal (58% versus 42%). In addition, 18 women in the Janssen vaccine subgroup reported heavy cycles in the post-vaccination period. Also, 70% of women in the Janssen vaccine subgroup reported a change in quality of life. According to the authors, "A plausible theory for [menstrual blood volume alteration] is extrapolated from the pathophysiology of patients with abnormal uterine bleeding due to increased volume. In these patients, a marked expression of macrophages and endometrial leukocytes capable of secreting powerful vasodilators is observed, explaining the increased volume of bleeding in patients." Based on the information available then in the Company Signal Tracking System, "On 23 Feb 2022 a signal was identified for Menstrual cycle and uterine bleeding disorders and Postmenopausal haemorrhage with the use of COVID-19 VACCINE AD26.COV2.S based on an aggregate review of post marketing data reported in the Company database and the Food and Drug Administration Vaccine Adverse Event Reporting System database." The rationale for creating the signal was "[...] the impact of the events on patient quality of life and the fact that is a safety topic with regulatory interest." However, following the review of data from the Global Safety database and the Food and Drug Administration (FDA) Vaccine Adverse Event Reporting System (VAERS), menstrual cycle and uterine bleeding disorders and post-menopausal haemorrhage safety signal was not validated due to
lack of sufficient evidence to establish an association. The current study has several limitations (study design, information and selection biases). Given the study limitations and limited information, no safety signal was identified at this time.

Rapporteur assessment comment:

This retrospective survey on social networks was responded by 408 women who met the inclusion criteria, of which 184 reported menstrual alteration on one occasion (i.e., frequency, regularity, duration and volume). It is agreed with the MAH that the study has multiple limitations, and no conclusion can be drawn.

Sa S, Lee CW, Shim SR, et al. The Safety of mRNA-1273, BNT162b2 and JNJ-78436735 COVID-19 Vaccines: Safety Monitoring for Adverse Events Using Real-World Data. Vaccine. 2022;10(2):320.

Abstract: Two mRNA COVID-19 vaccines (mRNA-1273, Moderna; and BNT162b2, Pfizer-BioNTech) and 1 viral vector vaccine (JNJ-78436735, Janssen/Johnson and Johnson) are authorised in the US to hinder COVID-19 infections. We analysed severe and common AEs in response to COVID-19 vaccines using real-world, VAERS data. From 14 December 2020 to 30 September 2021, 481,172 (50.7 ± 17.5 years, males 27.89%, 12.35 per 100,000 people) individuals reported AEs. The median time to severe AEs was 2 days after injection. The risk of severe AEs following the 1 viral vector vaccine (OR = 1.044, 95% CI = 1.005 to 1.086) was significantly higher than that after the 2 mRNA vaccines, and the risk among males (OR = 1.374, 95% CI = 1.342 to 1.406) was higher than among females, except for anaphylaxis. For common AEs, however, the risk to males (OR = 0.621, 95% CI = 0.612 to 0.63) was lower than to females. In conclusion, we provided medical insight and clinical guidance about vaccine types by characterising AEs using real-world data.

In particular, COVID-19 mRNA vaccines are safer than viral vector vaccines with regard to coagulation disorders,

whereas inflammation-related AEs are lower in the viral vaccine. The risk-benefit ratio of vaccines should be carefully considered, and close monitoring and management of severe AEs is needed.

MAH Comment: The authors, "selected 25 severe AEs, one of which was death, on the advice of a focus group of 3 clinical experts" which are listed in table S2 of the article. The authors stated, "Following mRNA 1273, BNT162b2, and JNJ-78436735 administration, death was reported in 2286, 2005, and 447 cases, respectively. Although JNJ-78436735 reported fewer cases, the incidence per 100,000 people was 2 to 3 times higher than that after the mRNA vaccines" and for death "the odds ratio of the viral vector vaccine to the mRNA vaccines was 1.901 (CI=1.713-2.111)." Regarding reported associations with death across all 3 vaccines, the authors state, "multivariate logistic regression analysis for death after adjusting for sex (reference: female), age, symptom onset(number of days), and vaccine type (reference: BNT162b2) with severe AEs as covariates revealed that acute respiratory distress syndrome (OR=20.510, I=12.620-33.332, p<0.001), haemorrhagic stroke (OR=9.965, CI=6.406-15.499, p<0.001), and acute myocardial
infarction (OR=3.872, CI=2.794 5.366, p<0.001) were most significantly associated with post-vaccination mortality." Regarding event associations with death, the authors' Table 2 reports incidence rates per 100,000 population/study period for the Moderna, Pfizer, and Janssen vaccines, respectively, as follows: acute respiratory distress syndrome, 0.03, 0.02, and 0.11; haemorrhagic stroke, 0.05, 0.04, 0.24; acute myocardial infarction, 0.15, 0.13, and 0.29. Known limitations from the study were noted by the authors, including the voluntary and fragmentary nature of reporting from VAERS. Regarding the events associated with death with the Janssen COVID-19 vaccine, the authors referred to cases of acute respiratory distress syndrome associated with Janssen COVID-19 vaccine likely related to cases of COVID-19 infection reported prior to the implementation of the booster vaccination with Ad26.COV2.S vaccine (the study used data from US FDA VAERS database covering the period from 14 December 2020 to 30 September 2021). The higher incidence of events of haemorrhagic stroke are likely related to the events of thrombosis and thrombocytopenia which is now an established adverse reaction associated with Ad26.COV2.S vaccine. Another higher incidence was identified with cases of GBS also considered as ADR in the CCDS of the Ad26.COV2.S vaccine. The event of acute myocardial infarction is closely monitored by the Company as an adverse event of special interest (AESI), in addition, the Company conducted a cumulative review of events of coronary artery disease (CAD) including myocardial infarction to address a request from PRAC. The analysis of all available data, the weight of cumulative evidence is insufficient to support a causal association between CAD (including acute myocardial infarction [AMI]) and the Ad26.COV2.S vaccine. Key factors supporting this conclusion include lack of established biological plausibility, no increased risk observed from review of a large clinical trial dataset, and insufficient evidence from the biomedical literature, clinical trials, literature and aggregate post-marketing spontaneous reports and as well as RWE to support an association between the development of CAD (including AMI) and Ad26.COV2.S. The safety signal was not confirmed. The review of this study results did not identify any new safety information.

Rapporteur assessment comment:

The Authors used RWE from 14 dec 2020 to 30 sept 2021 to analyze severe and common AEs after vaccination with either mRNA vaccine (Comirnaty and Spikevax) or viral vector vaccine (Janssen). According to the Author, the mRNA vaccines appeared safer compared to Janssen with regard to coagulation disorders.

Several coagulation disorders and their association with adenoviral vector vaccines have been further investigated by PRAC in several procedures. Venous thromboembolism, TTS, immune thrombocytopenia are already included in the product information. No new safety concern is detected here.

Woodcock R. Bartels L. Preliminary Evidence of a Link between COVID-19 Vaccines and

Otologic Symptoms. MedRxiv. 2022.

Hypothesis: This study investigates whether US Centers for Disease Control and Prevention VAERS data suggest an association between vertigo, tinnitus, hearing loss, Bell's palsy and the COVID-19 vaccines administered in the US.
Background: Published case reports suggest a possible association between various otologic symptoms and the COVID-19 vaccines, but the only published analysis of VAERS data, which did not account for underreporting of late-appearing AEs, found no association between hearing loss and the vaccines.
Method: The incidence in VAERS of vertigo, tinnitus, hearing loss, and Bell's palsy associated with COVID-19 vaccinations administered between 14 December 2020 and 07 June 2021 was compared with published rates for the general population. To account for underreporting of late-appearing AEs, incidences were calculated using only the initial part of the observation period, during which reported events spike above expected events.
Results: The COVID-19 vaccines were associated with statistically significant increases in the incidence of vertigo, tinnitus, hearing loss, and Bell's palsy of 1,877, 50, 12, and 14 cases per 100,000, respectively. In relation to the mRNA-1273 or BNT162b2 vaccines, the Ad26.COV2.S vaccine was associated with a statistically significant excess incidence of vertigo, tinnitus, and hearing loss of at least 723, 57, and 55 cases per 100,000, respectively.
Conclusion: These results suggest an association between the COVID-19 vaccines and vertigo, tinnitus, hearing loss, and Bell's palsy. They also suggest that, with respect to vertigo, tinnitus, and hearing loss, the association is relatively strong for the Ad26.COV2.S vaccine.
MAH Comment: The authors present that the incidence of tinnitus, hearing loss, vertigo is significantly higher after Ad.26.COV2.S use. Three out of the 4 mentioned events (tinnitus, vertigo, and Bell's palsy) are listed in the CCDS's Adverse Reactions section. The authors of this article do not provide sufficient information regarding hearing loss. The observation lacks data about the type of hearing loss (sensorineural, conductive, mixed loss), cases' full auditory history, and examination performed (Weber, Rinne tests, pneumoscopy, pure tone, air, and bone conduction testing, etc.). No new safety information is detected at this time.

Rapporteur assessment comment:

VAERS data was used in this study to evaluate possible association between vertigo, tinnitus, hearing loss, Bell´s Palsy and the covid-19 vaccines that have been used in US. Dizziness is included at frequency rare in the SmPC. In addition, Facial paralysis (including Bell's palsy) and tinnitus are also included in the SmPC. No new safety concern is detected here.

Class effect literature

Hertel M, Schmidt-Westhausen AM, Wendy S, et al. Onset of Oral Lichenoid Lesions and Oral Lichen Planus Following COVID-19 Vaccination: A Retrospective Analysis of about 300,000 Vaccinated Patients. Vaccines (Basel). 2022;10(3):480.

Introduction: Onset of oral lichenoid lesions (OLL) or oral lichen planus (OLP) can be rare adverse reactions to vaccines. Recently, the first solitary cases were reported after COVID-19 vaccination. The aim of the present study was to assess if an increased frequency of OLL/OLP can be found after COVID-19 vaccination within a large real-world cohort. It was assumed that the incidence of OLL/OLP was significantly higher in subjects who received COVID-19 vaccine (cohort I) compared to individuals who were not vaccinated (cohort II).
Methods: Initial cohorts of 274,481 vaccinated and 9,429,892 not vaccinated patients were retrieved from the TriNetX database (TriNetX, Cambridge, Massachusetts, US), and matched for age, gender and the frequency of use of non-steroidal anti-inflammatory drugs, beta blockers, and angiotensin-converting enzyme inhibitors.
Results: After matching each cohort, we accounted for 217,863 patients. Among cohort I, 146 individuals experienced OLL/OLP within 6 days after COVID-19 vaccination (88 and 58 patients had received mRNA and adenovirus vector-based vaccines), whereas in cohort II, 59 patients were newly diagnosed with OLL/OLP within 6 days after having visited the clinic for any other reason. The risk of developing OLL/OLP was calculated as 0.067% vs. 0.027%, for cohorts I and II, whereby the risk difference was highly significant ($p < 0.001$; log-rank test). RR and OR were 2.475

(95%
CI = 1.829; 3.348) and 2.476 (95% CI = 1.830; 3.350), respectively.
Conclusion: The hypothesis was confirmed. Accordingly, the obtained results suggest that the onset of OLL/OLP is a rare ADR to COVID-19 vaccines, especially to mRNA vaccines. Thus far, it remains unknown if specific components of the formulations cause a type IV hypersensitive reaction corresponding to OLL, or if the immune response post vaccination triggers a T cell-driven autoimmune reaction directed against the basal layer of keratinocytes of the oral mucosa in terms of OLP. Although OLL and OLP are both classified as premalignant lesions, spontaneous remission may be expected
over time, at least in the case of OLL. Therefore, the presented findings should not place any limitation toward the use of COVID-19-vaccines in broad levels of the population
MAH Comment: Eighty-eight and 58 subjects who experienced OLL/OLP had received mRNA and adenovirus vector-based vaccines. As stated by the authors, "Despite the matching process, a difference in the proportion of the subjects using NSAIDs remained, [which means] that the distribution difference in the frequency of the use of NSAIDs between both cohorts cannot be eliminated." They also pointed out that "the presented analysis found cases of newly diagnosed OLL/OLP in which adenovirus vectors had been administered as well, [hence it could] be carefully assumed that the presentation of the viral spike protein to the hosts immune system might play a role in the pathological mechanism, causing OLL/OLP following COVID-19 vaccination." Both OLL and OLP "are classified as premalignant lesions with an augmented risk of transformation into an oral squamous cell carcinoma", however, the literature states that the magnitude of the risk of malignant transformation of OLP to oral squamous cell carcinoma is unclear. The prevalence of OLP is 1 to 3 % in the general population and an incidence is in the range of ~60 to 190 per 100,000 person-years (Nagao 2005). The incidence in general population of OLL is unknown. Taking into consideration the limitations of the study, as well as lack of differential diagnosis and missing information on cases, there is no new safety signal identified at this time.

Rapporteur assessment comment:

Occurrence of oral lichenoid lesions (OLL) or oral lichen planus (OLP) was investigated in vaccinated and unvaccinated subjects by using data from TriNetX database in US. 58 subjects that received adenoviral vector vaccine was reported to have OLL or OLP within 6 days after vaccination and 59 subjects in the unvaccinated group. No clinical information has been provided and differences in use of NSAID between the two groups are noted. No further conclusions can be drawn.

Ma Y, Xu G. New-Onset IgA nephropathy Following COVID-19 Vaccination. QJM: An International Journal of Medicine. 2022.

Abstract: COVID-19 pandemic, caused by SARS-CoV-2, has caused significant economic and health damage worldwide. Rapid vaccination is 1 of the key strategies to curb severe illness and death due to SARS-CoV-2 infection. Hundreds of millions of people worldwide have received various COVID-19 vaccines, including mRNA vaccines, inactivated vaccines and adenovirus-vectored vaccines, but the side effects and efficacy of most vaccines have not been extensively studied.
Recently, there have been increasing reports of immunoglobulin A nephropathy (IgAN) after COVID-19 vaccination, however, whether their relationship is causal or coincidental remains to be verified. Here, we summarise the latest clinical evidence of IgAN diagnosed by renal biopsy associated with the COVID-19 vaccine published by 10 July 2022 with the largest sample size and propose a hypothesis for the pathogenesis between them. At the same time, the new opportunity presented by COVID-19 vaccine allows us to explore the mechanism of IgAN recurrence for the first time. Indeed,
we recognise that large-scale COVID-19 vaccination has enormous benefits in preventing COVID-19 morbidity and mortality. The purpose of this review is to help guide the clinical assessment and management of IgA nephropathy post-COVID-19 vaccination and to enrich the 'multi-hit' theory of IgA nephropathy.

MAH Comment: The article presents 48 cases of IgA nephropathy from the literature. Patients received Pfizer, Moderna, and AstraZeneca vaccines. The authors state, "the patients [they] reported are from a single case study, and there is only a temporal association between symptom onset and COVID-19 vaccination in IgAN patients, and [they] are unable to infer a causal relationship between vaccine and IgAN". As per the Summary Safety Report (SSR) covering the period from 16 January 2022 through 15 March 2022, upon request from the WHO Uppsala monitoring centre on 22 February 2022 safety signal was opened and "comprehensive search of clinical and post marketing database for adverse event reports [was performed]. [...] Based on the review of evidence from cases from interventional clinical studies and post-marketing surveillance data, there [was] no evidence of causal association between the event of IgA nephropathy and vaccination with Ad26.COV2. S. vaccine". The presented reference does not provide additional evidence to the completed above described comprehensive review. No new safety information is detected at this time.

Rapporteur assessment comment:

The paper summarizes case reports of IgA nephropathy, mostly reported from Asia, in a total 48 persons of which 3 had received Vaxzevria (adenoviral vector vaccine).

A cumulative review was executed in EMEA/H/C/005737/MEA/014.9 SSR, in which no evidence of causal association between the event of IgA nephropathy and vaccination with JCovden was detected.

No new safety concern detected.

1.3.6. Lack of efficacy in controlled clinical trials

Although protection with a single-dose of Ad26.COV2.S in adults ≥18 years of age, including in adults ≥60 years of age against severe/critical COVID-19, including hospitalisations and deaths related to COVID-19, continued to be observed over time, across age groups, comorbidities, countries, regions, and emerging SARS-CoV-2 variants, including variants of concern/variants of interest (variants of concerns (VOC)/VOIs), there was a trend towards a decreased protection against moderate to severe/critical COVID-19 over time. Protection against moderate to severe/critical COVID-19 varied by (newly) emerging SARS-CoV-2 variants, including VOCs/VOIs, throughout the trial, and this potentially contributes to the observed decrease, although waning protection of Ad26.COV2.S cannot be excluded. Efficacy results from the
primary analysis of ongoing Phase 3 trial VAC31518COV3009, in which an Ad26.COV2.S booster dose was administered 2 months after the first vaccination, suggest that protection against moderate to severe/critical COVID-19 (including against SARS-CoV-2 VOC) and severe/critical COVID-19 increased after a homologous booster dose administered 2 months after the single-dose primary vaccination. When considering the VE against SARS-CoV-2 variants, including VOCs/VOIs, observed in Trial VAC31518COV3001, caution is needed when interpreting data where there were (too) few COVID-19 cases and/or CIs were wide. Differences were observed in protection against moderate to severe/critical COVID-19. No reduction in VE estimates compared to that of the reference strain (VE estimate [95% CI]: 58.2% [34.96; 73.72] at least 28 days after vaccination) for the Alpha VOC and other variants was observed, while the VE estimates for the Delta, Gamma VOCs, Mu, Lambda VOIs were reduced (<36%). The VE estimate (95% CI) for the Beta VOC, at least 28 days after vaccination was 51.9% (19.06; 72.19). For severe/critical COVID-19, the VE estimates were 63% to 91% across variants with sufficient COVID-19 cases, such as Beta, Gamma VOCs, and Lambda, Mu VOIs. In summary, in the double-blind randomised placebo-controlled trial, a single-dose of Ad26.COV2.S provided at least 6 months of protection against severe/critical disease, hospitalisation, and death, with varying degrees of protection against symptomatic disease depending on the variant. Since the clinical trial VE estimates are below 100%, particularly for mild and moderate disease, breakthrough cases in vaccinated individuals are

expected to occur.
Altogether, the totality of data allows us to conclude that vaccination with Ad26.COV2.S remains efficacious against severe/critical COVID-19, including hospitalisations and deaths related to COVID-19, including against some variants. While the analysis of Delta cases from clinical trials remains inconclusive, multiple sources of evidence confirm vaccine effectiveness against observed COVID-19 and COVID-19-related hospitalisation related to the Delta and Omicron VOC in a real-world setting.

Rapporteur assessment comment:

Reduced VE has been observed for variants (i.e. Delta, Gamma, Mu and Lambda) compared to Alpha strain. No information regarding effectiveness against omicron variants have been presented.

1.3.7. Late-breaking information

Thrombocytopenia and Single Organ Cutaneous Vasculitis

On 31 August 2022, both thrombocytopenia and single organ cutaneous vasculitis were identified to have an association with Ad26.COV2.S from the review of the VAC4EU COVID vaccine safety monitoring system. Both events are already listed as adverse reactions following earlier assessments from the EMA PRAC as immune thrombocytopenia and cutaneous small vessel vasculitis respectively. After the data lock point, the Company opened a safety signal based on the disproportionate reporting of vasculitis, particularly cutaneous vasculitis. The evaluation of this signal is ongoing and will be presented in the next PBRER.

Rapporteur assessment comment:

The opening of a new signal regarding cutaneous vasculitis by the MAH is noted, and it will be presented in the next PSUR.

Furthermore, after the reporting interval, a paper based on epidemiological data from the US published where the risk for postural orthostatic tachycardia syndrome (POTS) after covid-19 vaccination was investigated(Kwan, A.C., Ebinger, J.E., Wei, J. et al. Apparent risks of postural orthostatic tachycardia syndrome diagnoses after COVID-19 vaccination and SARS-Cov-2 Infection. Nat Cardiovasc Res (2022)). For the next PSUR, the MAH is asked to discuss this issue.

On 17 February 2023, the MAH informed EMA that the U.S. FDA had on 14 Feb 2023 requested to update the JCOVDEN EUA fact sheet to include new W&P for myocarditis and pericarditis. The MAH also stated that based on the totality of safety data available, there is at present insufficient evidence to establish a causal association between Ad26.COV2.S and the occurrence of cardiac inflammatory disorders (incl. Myocarditis and Pericarditis). The MAH continues to monitor both conditions as AESIs as defined in the RMP and will provide an updated and detailed analysis in the upcoming PSUR. Given previous thorough assessments, this is considered sufficient. See also 2.3.1

On 31 March 2023, the MAH submitted updated information on this topic, in the form of an Emerging Safety Issue (ESI). They state that they, following the FDA request, have performed a full analysis of the available safety data for myo/pericarditis. They conclude that data available to the DLP for the next PSUR (24 February 2023) show an increase in the risk for myocarditis and pericarditis following Ad26.COV.S vaccination, particularly in males under the age of 40 in the first two weeks following vaccination, with the highest risk at 7 days. They also conclude that this suggests that there is a reasonable possibility of a causal association between Ad26.COV2.S and myocarditis and pericarditis. The MAH proposes to add myocarditis and pericarditis as an Important Identified Risk in the RMP, and states that it will be included as ADR in the company core data sheet and that a warning text also will be added. The MAH also proposes to submit a proposal for an updated product information and for the RMP in the next PBRER

package (due for submission on 5 May 2023 - DLP 24 February 2023). See section 2 Assessment conclusions and actions, and also 2.3.1 in the Annex.

2. Signal and risk evaluation

2.1. Summary of safety concerns

At the beginning of the reporting period

The summary of safety concerns (ie, important identified risks, important potential risks, and missing information) at the beginning of the reporting period to be included in the Ad26.COV2.S PBRER are based on cRMP (version 4.0 dated 09 December 2021) and are summarised in Table 61.

Table 61: Important Identified Risks, Important Potential Risks and Missing Information at the Beginning of the Reporting Period in the Core Risk Management Plan

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[a] Immune thrombocytopenia[b]
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

Key: cRMP=Core Risk Management Plan; ITP=Immune thrombocytopenia
a: Venous thromboembolism has been reclassified as an important identified risk. The cRMP is in the process of being updated to reflect the reclassification.
b: ITP is comparable to thrombocytopenia, including ITP in the European Risk Management Plan.

At the end of the reporting period

- During the reporting period, the safety concerns were re-evaluated. The updated summary of safety
  concerns which was based on the cRMP is presented below in Table 62.
  The cRMP version 4.0 was updated to version 5.0 on 24 May 2022 with the removal of the safety concern of Anaphylaxis which was previously classified as an important identified risk. (EMEA/H/C/PSUSA/00010916/202108)

Table 62: Important Identified Risks, Important Potential Risks and Missing Information at the End of the Reporting Period in the Core Risk Management Plan

Important Identified Risks	Thrombosis with thrombocytopenia syndrome Guillain-Barré syndrome
Important Potential Risks	Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) Venous thromboembolism[a] Immune thrombocytopenia[b]
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

Key: cRMP=Core Risk Management Plan; ITP=Immune thrombocytopenia
a: Venous thromboembolism has been reclassified as an important identified risk. The cRMP is in the process of being updated to reflect the reclassification.
b: ITP is comparable to thrombocytopenia, including ITP in the European Risk Management Plan.

Rapporteur assessment comment:

Anaphylaxis has been removed from the list of important identified risk and the RMP has been uppdated accoridningly in other procedure.

2.2. Signal evaluation

2.2.1. Ongoing Signals

There were no signals that were undergoing evaluation at DLD of this report.

2.2.2. Regulatory Authority Requested Topic

Glomerulonephritis and Nephrotic Syndrome

Request: According to the PRAC Final Assessment Report (FAR) (PRAC AR 2022) for the Ad26.COV2.S PBRER (EMEA/H/C/PSUSA/00010916/202202) received on 29 September 2022, the MAH was requested to address the following in the current report:
"A cumulative review of glomerulonephritis and nephrotic syndrome should be submitted. This should include a search conducted at the level of HLT "glomerulonephritis and nephrotic syndrome".
Furthermore, the MAH should provide relevant data from the literature and clinical trials. The MAH should provide causality assessments, and based on these data, discuss the need for updating the product information and/or risk management plan, and submit proposals as required."

MAH Conclusion: The Company conducted a comprehensive cumulative review of glomerulonephritis and nephrotic syndrome per the above PRAC request. Based on the totality of cumulative post-marketing and clinical trial data and comprehensive literature review, there is insufficient information to suggest an association between Ad26.COV2.S and the occurrence of glomerulonephritis and nephrotic syndrome.
Supporting conclusions from this report were:
• no clear mechanism of action (MOA) has been established in association with any vaccine although possible MOA have been suggested.
• no cases occurred in the Ad26.COV2.S group during the double-blind phase of the pooled analysis. For all ongoing Ad26.COV2.S clinical trials, covering the period beyond the double-blind pooled analysis, there were 3 participants who experienced a "glomerulonephritis and nephrotic syndrome" following Ad26.COV2.S vaccination during the open-label phase. All 3 cases were considered 'not related' by the investigator and had an onset beyond day 90 post-vaccination.
• insufficient evidence regarding an association role of the Ad26.COV2.S vaccine and glomerulonephritis and nephrotic syndrome based on the review of post-marketing data.

• both disproportionality datamining and RWE rapid cycle analysis were not conclusive because data was not consistent across data sources. • O/E ratio <1 across the broad analysis, inconsistent pattern was identified for the sensitivity and restricted analysis in terms of age, gender and region. The Company will continue to monitor glomerulonephritis and nephrotic syndrome via routine pharmacovigilance activities.

Rapporteur assessment comment:

In the previous PSUR there was a request to present a cumulative review of Glomerulonephritis and Nephrotic Syndrome as supplementary information. The MAH responded within the last PSUR presenting a cumulative review on all cases of GN and NS. Data have been also submitted with this PSUR. Based on these data, the PRAC concluded that there was no need for additional actions.

Severe Cutaneous Reactions

On 30 May 2022, the Company received a request from the Uppsala Monitoring Centre (UMC) to provide a comment on their observed signal (based on WHO VigiBase data) on severe cutaneous adverse reactions (SCAR). This topic had been discussed in detail in the previous PBRER (DLD of 24 February 2022), where the Company concluded there was insufficient evidence to associate SCAR or Erythema multiforme to Ad26.COV2.S. The Company submitted the results of this evaluation to UMC, this topic is considered closed and refuted. In the PRAC FAR (EMEA/H/C/PSUSA/00010916/202202), for the Ad26.COV2.S PBRER dated
25 August 2021 to 24 February 2022, PRAC indicated that routine monitoring is sufficient.

Rapporteur assessment comment:

In the previous PSUSA, there was a request to present a cumulative review of severe cutaneous reactions. The MAH responded within the last PSUSA, and the PRAC thereafter concluded that there was no need for additional actions and that routine monitoring will be sufficient ahead.

For the clinical overview submitted within the latest renewal procedure, it was concluded that : "Severe cutaneous adverse reactions, were evaluated in the PRAC PSUR assessment report (EMEA/H/C/PSUSA/00010916/202202; period covered by the PSUR: 24/08/2021 To: 24/02/2022). No new safety concern was detected. Nevertheless, an updated cumulative review should be presented with the next PSUR."

The MAH therefore suggest to perform a gap analysis from 25 February 2022 to 24 February 2023 inclusive high level analysis of post-marketing cases and the literature regarding SCAR and to present results with the next PSUR **(next PSUR)**. This is endorsed.

Neuralgic Amyotrophy

The search of the Company global safety database retrieved a total of 15 cases of NA following vaccination with Ad26.COV2.S between 25 February 2022 to 24 August 2022. Of the 15 cases, 14 were non-booster cases received from post-marketing sources and the remaining 1 booster case was received from the VAC31518COV3001 clinical trial. The cases were received from Netherlands (n=4), France (n=3), Germany (n=2), South Africa (n=2), US (n=2), Portugal (n=1), and Switzerland (n=1) which concerned 9 males and 6 females aged 21 to 75 years who experienced the EOIs of neuralgic amyotrophy (n=13) or radiculitis brachial (n=2). Of the 15 cases, 53.3% (8/15) were medically confirmed while the remaining 47% (7/15) were medically unconfirmed. The TTO was reported as "on the same day" to 160 days following vaccination with Ad26.COV2.S. There were no EOIs with a fatal outcome. The outcome for the EOIs were reported as not resolved (n=11), resolving (n=2), resolved (n=1), and unknown (n=1).

Of the 15 cases, 8 were excluded from the analysis as the EOI: neuralgic amyotrophy (n=7) and radiculitis brachial (n=1) occurred outside of the 28 day risk window (TTO reported between 32 to 160 days) following exposure to Ad26.COV2.S. Of the 7 remaining cases, 1 nonserious case was further excluded from the analysis due to the 21-year-old female patient's confounded medical history of NA and

an unspecified TTO.

Of the remaining 6 cases, follow-up was received during the period covered by this report for 2 cases [redacted] and [redacted] which were previously presented in the PBRER covering the period from 25 August2021 to 24 February2022. In [redacted] it was reported that the patient still experienced pain in the left arm including wrist and fingers, and in [redacted], it was reported that the patient had not recovered from scapula alata, NA, and the outcome for the events of pain in arm and numbness in leg were not reported. These 2 cases were also excluded from further analysis as the follow-up information did not impact the initial MAH assessment based on the van Alfen diagnostic criteria. Details of the 4 cases reporting neuralgic amyotrophy have been summarised in table 1 below.

Table 1: Selected Spontaneous Cases of Neuralgic Amyotrophy Following Vaccination With Ad26.COV2.S Captured in the Global Safety Database From 25 February 2022 Through 24 August 2022 (n=4)

AER# Age (Years)/Sex Country/Territory Medically Confirmed (Yes/No)	Event of Interest[a]	Latency (Days)[b]	MedDRA PT Outcome[c]	Concomitant Medications	Relevant Medical History/ Concurrent Conditions	Brief Description *MAH Comment*
[redacted] 66/Female [redacted] Yes	*Neuralgic amyotrophy*	13	Not resolved	NR	NR	Approximately 13 days following vaccination with Ad26.COV2.S, the patient experienced NA (Parsonage-Turner syndrome). At the time of reporting, the EOI was not resolved. No additional details regarding the patient's concurrent/past medical history, concomitant medications, relevant clinical data including supportive diagnostic testing, nor clinical course including treatment were provided. ***MAH Comment**: None of the diagnostic criteria were met. While there was limited information, based on the temporal relationship of the reported event to vaccine, a causal relationship was considered as possible to vaccine.*
[redacted] 75/Male [redacted] Yes	*Neuralgic amyotrophy*	NR	Not resolved	NR	COVID-19 test positive (date unspecified)	It was reported that the patient was diagnosed with NA at an unspecified time following vaccination with Ad26.COV2.S. Medical history was positive for COVID-19. At the time of reporting, the EOI was not resolved. No additional details regarding the patient's concurrent/past medical history, concomitant medications, relevant clinical data including supportive diagnostic testing, nor clinical course including treatment were provided. ***MAH Comment**: None of the diagnostic criteria were met. While there was limited information, , a causal relationship was considered as possible to vaccine.*
[redacted] 57/Male [redacted] No	*Neuralgic amyotrophy*	Same day	Not resolved	NR	COVID-19 test positive (date unspecified)	On the same day following vaccination with Ad26.COV2.S, the patient experienced NA (Parsonage-Turner syndrome).. At the time of reporting, the EOI was not resolved. No additional details regarding the patient's concurrent/past medical history, concomitant medications, relevant clinical data including supportive diagnostic testing, nor clinical course including treatment were provided. It was reported that the patient tested positive for COVID-19 approximately 314 days following vaccination with Ad26.COV2.S. ***MAH Comment**: None of the diagnostic criteria were met. While there was limited information, based on the temporal relationship of the reported event to vaccine, a causal relationship was considered as possible to vaccine.*
[redacted] 64/Female [redacted] Yes	*Neuralgic amyotrophy* Fatigue Pain Myalgia Paraesthesia	Same day	Not resolved	NR	NR	On the same day following vaccination with Ad26.COV2.S, the patient experienced brachial plexus neuritis, pain upon movement, myalgia, and paraesthesia of the upper limb. The patient was hospitalised at an unspecified time following vaccination with Ad26.COV2.S and subsequently experienced exhaustion. At the time of reporting, all events were not resolved. ***MAH Comment:** One of 4 diagnostic criteria was met. This case described new onset upper limb pain upon movement,myalgia and paraesthesia. Pain score, upper extremity movement, and clinical course were not*

						described. Based on the symptoms consistent with NA in this medically confirmed case, this can be considered a possible case per van Alfen 2015[d] criteria. Based on the temporal relationship with vaccination, the causality was considered as possibly related.

Key: AER#=Adverse Event Report Number; COVID-19=Coronavirus Disease-2019; EOI=Event(s) of Interest; MAH=Marketing Authorisation Holder; MedDRA=Medical Dictionary for Regulatory Activities; n=Number; NA=Neuralgic Amyotrophy; NR=Not Reported; PT=Preferred Term

a: The MedDRA PTs of interest and their seriousness have been italicised.

b: Latency has been calculated from the vaccine administration to the onset of event of interest.

c: The outcome has been presented for the event of interest only.

d: van Alfen N, van Eijk JJ, Ennik T, et al. Incidence of Neuralgic Amyotrophy (Parsonage Turner Syndrome) in a Primary Care Setting - A Prospective Cohort Study. PLoS ONE. 2015;10(5):1-9.

MAH Conclusion

Based on the totality of data reviewed from the Company global safety database there is insufficient evidence to establish a causal role of the Ad26.COV2.S vaccine in the occurrence of NA. Although the temporal relationships of the reported events to the vaccine in the 3 cases identified indicate that a causal relationship to the vaccine at individual case level is possible, diagnostic criteria specific to NA were not consistently demonstrated in the cases overall. No change to the product label is warranted.
Key factors to support this conclusion include:
• low number of cases reported cumulatively through 24 August 2022 (n=29) following a total of 52,684,577 doses of Ad26.COV2.S administered worldwide since launch.
• none of the 4 serious cases identified within the reporting period met the van Alfen diagnostic criteria for definitive or probable NA. However, 1 case met one of the 4 van Alfen diagnostic criteria and thus was assessed as possibly related.
• many of the cases contained limited information regarding relevant clinical data including supportive diagnostic testing, clinical course, concomitant medications/vaccinations, relevant concurrent conditions/ medical history, duration of the event, and treatment; thus, precluding a thorough medical assessment.
This topic will continue to be monitored via routine pharmacovigilance activities.

Rapporteur assessment comment:

In the previous PSUSA; there was a request to present a cumulative review of neuralgic amyotrophy. In total, 29 cases have been identified cumulatively and 15 cases during the reporting interval. Of the 15 cases identified in the interval, 4 cases were identified, showing a symptom pattern typical for amyotrophic neuralgia and a reasonable TTO (van Alven). The MAH has presented these cases in a tabular format above.

Based on the given information, the MAH's conclusion is agreed.

Vasculitis

According to the PRAC FAR (PRAC AR 2022) for the Ad26.COV2.S PBRER (EMEA/H/C/PSUSA/00010916/202202) received on 29 September 2022, the MAH was requested to address the following in the current report: "In the last SSR, (EMEA/H/C/005737/MEA/014.9), a request to provide continued detailed presentation of vasculitis cases, particularly those with systemic manifestations, was made for the next PSUR. The MAH will include address this in the next PSUR (DLP 24 August 2022). This is endorsed."

Results: During the interval reporting period of 25 February2022 to 24 August 2022, 27 (13 medically confirmed and 14 medically unconfirmed) initial, primary dose cases reporting vasculitis were identified. Of these 27 cases, 20 were serious and 7 were nonserious and reported a total of 29 EOI (17 serious; 12 nonserious). Of these 27 initial, primary dose cases received during the interval reporting period, all were reported from post-marketing sources (including spontaneous and solicited). No cases were reported from Janssen Sponsored or Janssen Supported Clinical Studies.

Cumulatively, 160 (99 medically confirmed and 61 medically unconfirmed) primary dose cases reporting vasculitis were identified. Of these cases, 130 cases were serious and 30 were nonserious and reported a total of 168 EOI (124 serious; 44 nonserious). Of the 160 cumulative primary dose cases received, 1 was reported from a Janssen Sponsored Clinical Study, 3 from Janssen Supported Clinical Studies, and 156 from post-marketing sources (including spontaneous and solicited cases). Among the 156 primary dose cases, 6 reported limited information on multiple patients with little or no information on the TTO, course of events, demographics of individual patients and they are excluded from further analysis. Of the remaining 150 cases, 121 were serious and 29 were nonserious and reported a total of 157 EOI(117 serious; 40 nonserious).

Table 2: Frequency of MedDRA PTs of Interest in Post-marketing, Primary Dose Cases Reporting Vasculitis With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Vasculitis	6	9	31	27
Polymyalgia rheumatica	5	0	25	0
Cutaneous vasculitis	4	0	23	0
Henoch-Schonlein purpura	1	1	11	2
Arteritis	0	1	1	1
Granulomatosis with polyangiitis	1	0	1	0

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: The MedDRA PTs of interest have been sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event of interest.

During the reporting period of 25 February 2022 to 24 August 2022, one initial, fatal case of small -vessel vasculitis with potential systemic manifestations was reported (the 35-year-old female had a fatal EOI of granulomatosis with polyangiitis [Wegener's granulomatosis] and vasculitis on an unreported day post-vaccination).

During the reporting period, six serious spontaneous non-fatal cases reported small-vessel vasculitis and among these, 5 had systemic manifestations.

Booster dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 4 (1 medically confirmed and 3 medically unconfirmed) initial cases reported as booster were identified. There were 4 serious casesreporting a total of 4 serious EOI. There were no nonserious cases reported. Of these cases, 2 were heterologous and 2 were homologous. All the 4 cases reported as booster during the interval were reported from post-marketing sources.

Cumulatively, 11 (3 medically confirmed and 8 medically unconfirmed) cases reported as booster were identified. Of these cases, 9 were serious and 2 were nonserious and reported a total of 11 EOI (8 serious; 3 nonserious). Of these cases, 4 were heterologous and 7 were homologous. All 11 cumulative cases reported as booster were reported from post-marketing sources.

Table 5: Frequency of MedDRA PTs of Interest in Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Vasculitis

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Cutaneous vasculitis	3	0	3	0
Erythema induratum	1	0	1	0

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: The MedDRA PTs of interest have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022).

During the interval reporting period of 25 February 2022 to 24 August 2022, there were no booster cases with systemic manifestations and there were no fatal cases reported as booster retrieved from the search of the Company global safety database.

MAH Conclusion, vasculitis: Following the review of both cumulative and interval reporting data, no changes are currently warranted to the prescribing information. The Company will continue to closely monitor cases of vasculitis, especially cases of small vessel vasculitis with systemic manifestations, and cases with medium- and large-vessel vasculitis

Rapporteur assessment comment:

During the interval reporting period of 25 February 2022 to 24 August 2022, 27 (13 medically confirmed and 14 medically unconfirmed) initial, primary dose cases reporting vasculitis were identified from post-marketing sources. Of these, 20 were serious and 7 were nonserious and reported a total of 29 EOI (17 serious; 12 nonserious). During the reporting period, one fatal case that included small-vessel vasculitis was reported, and six serious spontaneous non-fatal cases reported small-vessel vasculitis, of these 5 had systemic manifestations.

In the PRAC Assessment Report dated 08 March 2022 (EMA/PRAC/138923/2022) of the procedure EMEA/H/C/005737/MEA/014.8, in which a variation was requested to update section 4.8 of the SmPC to include "cutaneous small vessel vasculitis" as ADR related to COVID-19 Vaccine Janssen and to update section 4 of the PIL accordingly which was implemented in EMEA/H/C/005737/IB/0051.

It is noted that the company has opened a signal on cutaneous vasculitis after the data lock point of this PSUR. This further review will be presented and assessed in the next PSUR.

Thrombosis with Thrombocytopenia Syndrome

According to the PRAC FAR (PRAC AR 2022) for the Ad26.COV2.S PBRER (EMEA/H/C/PSUSA/00010916/202202) received on 29 September 2022, the MAH was requested to address the following in the current report:

"Given the removal lot XD955 in April 2022, and concerns from one member state of more reports of suspected ADRs for this batch than expected, and particularly in relation to TTS, the MAH should provide a summary of number of reported TTS cases, per specific batch number. The concerns that some quality problem with this batch could be involved in development of serious ADRs should also be addressed."

Post-marketing

Cumulatively, there were 227 primary dose cases received from post-marketing sources (including spontaneous and solicited cases) that reported at least 1 thromboembolic event and thrombocytopenia or decreased platelet count. An overview of the cumulative cases is presented in Section Thrombosis with Thrombocytopenia Syndrome.

Of these, 108 cases did not report any batch number. The remaining 119 cases reported a batch number, which includes patient demographics, serious events, outcomes per case, and diagnostic criteria (BC/CDC/PRAC). Most cases were reported from the US (n=74) and Germany (n=11). Cases reported several events, and the more frequently reported events were cerebral venous sinus thrombosis, pulmonary embolism, deep vein thrombosis and/or thrombocytopenia and platelet count decreased. Of note, only 7 cases reported the PT Thrombosis with thrombocytopenia syndrome. The outcome for most cases was not reported or not resolved. There were no trends regarding the diagnostic criteria.

There were 18 cases with a fatal outcome. The cases regarding the 13 females (39- to 79-years- old) were from the US (n=10; batch 1802070, 1805022, 1805025, 1805020, 1805029), Spain (n=2; batch 21C19-01 and XE423) and France (n=1; batch 21C14-03). In cases regarding the 4 males (27- to 66-years old) were from Germany (n=2; batches XD974, XE395), and 1 each for Spain (batch 21C17-04)

and US (batch 041A21A). There was 1 case from Poland in a 43-year-old patient (sex not reported) and the batch number was XE423. Regarding batch number XD955, there was only 1 case which concerned a 42-year-old male who experienced the serious events of deep vein thrombosis in the lower left limb, embolism (also noted as pulmonary embolism) and thrombocytopenia 42 days after receiving the Ad26.COV2.S vaccine. The patient was hospitalised for an unspecified duration and treatment details were not provided. There was no information regarding the patient's past medical history or concurrent conditions or concomitant medications. The outcome for each event was not resolved. (BC 5, CDC Neither [Non-tier 1/2)], PRAC Possible).

MAH Conclusion

Upon review of post-marketing cases reporting a batch number and at least a 1 serious event, the batch analysis did not reveal quality concerns that could be linked to serious adverse reactions, including TTS.

Rapporteur assessment comment:

The MAH has provided the requested information. No new safety concern is detected here.

Use with concomitant vaccination

During the interval reporting period of 25 February 2022 to 24 August 2022, 23 (7 medically confirmed and 16 medically unconfirmed) post-marketing sources (including spontaneous and solicited), initial, primary dose cases reporting the use with concomitant vaccination were identified. Of these 23 cases, 12 were serious and 11 were nonserious and reported a total of 88 events (25 serious; 63 nonserious). Of these 23 post-marketing, initial, primary dose cases, the most frequently reported countries/territories of origin (n≥6) were Brazil (n=8), followed by the US (n=6). These cases concerned 11 males, 10 females, and 2 did not report sex. The age range was from 30 to 95 years.

Cumulatively, 97 (28 medically confirmed and 69 medically unconfirmed) post-marketing sources (including spontaneous and solicited), primary dose cases reporting the use with concomitant vaccination were identified. Of these cases, 43 cases were serious and 54 were nonserious and reported a total of 455 events (125 serious; 330 nonserious).

The most commonly reported co-administered vaccine type (both during the reporting period as well as cumulatively) was the influenza vaccine (interval n=18; cumulatively n=56).

Table 24: Frequency of MedDRA PTs in Post-marketing, Primary Dose Cases Reporting Use With Concomitant Vaccination With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Pyrexia	1	7	1	20
Fatigue	0	4	1	16
Suspected COVID-19	0	4	1	5
Vaccination failure	4	0	10	0
Arthralgia	0	3	1	9
Diarrhoea	0	3	1	6
Myalgia	0	3	0	8
Pain	0	3	2	8
Pulmonary embolism	3	0	4	0

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

a: The MedDRA PTs with a frequency ≥3 have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event.

During the reporting period of 25 February 2022 to 24 August 2022, 4 post-marketing, primary dose fatal cases with 11 fatal events were retrieved. The fatal event was pulmonary embolism, which occurred in 3 elderly patients (aged 71, 78 and 95 years) who received influenza vaccine on the same day as Ad26.COV2.S. The remaining case involved an adult patient (aged 51 years), with underlying alcohol addiction, nicotine abuse, chronic obstructive pulmonary disease (COPD), and alcoholic steatohepatitis,

who experienced general physical health deterioration, hypoglycaemia, hypoxia, multiple organ dysfunction syndrome, pyrexia, respiratory failure, resuscitation, and tachycardia. The patient had received the diphtheria, pertussis, polio and tetanus vaccines, 1 month and 17 days after Ad26.COV2.S administration. No information on concomitant medication and clinical course/diagnosis of the events was provided.

Booster dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 36 (7 medically confirmed and 29 medically unconfirmed) post-marketing sources (including spontaneous and solicited), initial cases reported as booster were identified. There were 13 serious and 23 nonserious cases and reported a total of 226 events (38 serious; 188 nonserious). Of these cases, 28 were heterologous and 8 were homologous. The most frequently reported countries/territories of origin (n≥5) were Brazil (n=27), followed by the US (n=5). These cases concerned 21 females, 14 males, and 1 did not report sex. The age range was from 13 to 81 years.

Cumulatively, 60 (9 medically confirmed and 51 medically unconfirmed) post-marketing sources (including spontaneous and solicited) cases reported as booster were identified. Of these cases, 26 were serious and 34 were nonserious and reported a total of 347 events (72 serious; 275 nonserious). Of these cases, 38 were heterologous and 22 were homologous.

The most commonly reported co-administered vaccine type (both during the reporting period as well as cumulatively) was the influenza vaccine (interval n=34; cumulatively n=56).

Table 27: Frequency of MedDRA PTs in Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Use With Concomitant Vaccination

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Off label use	0	24	0	26
Inappropriate schedule of product administration	0	13	0	15
Fatigue	0	12	1	16
Pyrexia	1	11	2	14
Headache	0	10	2	13
Dizziness	0	8	1	9
Injection site pain	0	7	0	11
Malaise	0	7	0	8
Chills	0	6	1	9
COVID-19	1	4	2	7
Myalgia	0	5	0	6
Arthralgia	0	4	0	7
Asthenia	0	4	0	5
Feeling abnormal	0	4	0	6

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

a: The MedDRA PTs with a frequency ≥4 have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event.

During the reporting period of 25 February 2022 to 24 August 2022, 1 initial, fatal case reported as booster with 1 fatal event was retrieved. The fatal event was acute respiratory distress syndrome which occurred in the context of pulmonary embolism and COVID-19 infection.

MAH Conclusion: Most of the events reported in patients receiving Ad26.COV2.S with concomitant vaccines were reactogenic and/or listed for Ad26.COV2.S. No trend in events, including those with fatal outcome
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:

No new safety concern was detected for this item.

Vaccination anxiety-related reactions

During the interval reporting period of 25 February 2022 to 24 August 2022, 1,029 (489 medically confirmed and 540 medically unconfirmed) initial, primary dose cases reporting vaccination anxiety-related reactions were identified. Of these 1,029 cases, 620 were serious and 409 were nonserious and reported a total of 1,181 EOI (647 serious; 534 nonserious). Of the 1,029 primary dose cases, 308 met the criteria as vaccination anxiety-related reactions. Of the 308 cases, 253 were medically confirmed and 251 cases were serious. Of these 308 primary dose cases meeting criteria for vaccination anxiety-related reactions during
the interval reporting period, all were from post-marketing sources (including spontaneous and solicited cases). No cases were from Janssen Sponsored Clinical Studies or Janssen Supported Clinical Studies.

Cumulatively, 5,064 (1,644 medically confirmed and 3,420 medically unconfirmed) primary dose cases reporting vaccination anxiety-related reactions were identified. Of these cases, 2,656 were serious and 2,408 were nonserious and reported a total of 5,735 EOI (2,623 serious; 3,112 nonserious). Of the 5,064 cumulative cases, 1,210 met the criteria as vaccination anxiety-related reactions. Of the 1,210 cases, 791 were medically confirmed and 902 were serious.

Booster dose

Cumulatively, 158 (32 medically confirmed and 126 medically unconfirmed) cases reported as booster were identified. Of these cases, 75 were serious and 83 were nonserious and reported a total of 183 EOI (56 serious; 127 nonserious). Of the 158 cumulative cases, 9 met the criteria as vaccination anxiety-related reactions. Of the 9 cases, 3 were medically confirmed and 4 were serious. Of these cases, 7 were homologous and 2 were heterologous.

MAH Conclusion: A review of the cases of anxiety-related reactions identified in the current interval confirmed these are consistent with the known safety data for these events including rapid TTO and typically
transient in nature. Anxiety-related reactions were previously assessed as a signal for Ad26.COV2.S and it has been concluded that these anxiety-reactions to immunisation are a complication of the immunisation
process. The CIOMS/WHO Working Group on Vaccine Pharmacovigilance notes that the types of reactions caused by vaccination anxiety include but are not limited to vasovagal mediated reactions, hyperventilation mediated reactions, and stress-related psychiatric disorders. Based on a review of all available data, no new safety issues were identified for vaccination anxiety-related reactions. Vaccination anxiety-related reactions such as syncope will be discussed in future PBRERs in line with the GVP Module on Vaccines (Product- or Population-Specific Considerations I: Vaccines for prophylaxis against infectious diseases).

Rapporteur assessment comment:

A warning regarding the possibility of anxiety related reactions is already included in section 4.4 of the SmPC. No new safety concern is detected here.

Vaccine failure

During the interval reporting period of 25 February 2022 to 24 August 2022, 4,950 post-marketing (4,672 medically confirmed and 278 medically unconfirmed) primary dose cases reporting events of

vaccine failure or LOE were identified. Of these 4,950 cases, 4,711 were serious and 239 were nonserious and reported a total of 9,522 EOI (9,138 serious, 384 nonserious). Of these 4,950 cases, the most frequently reported country/territory of origin was Austria (n=4,345) followed by the US (n=260) and Iceland (n=69). Of the 4,950 cases, 2,925 cases concerned males, 1,903 females, and 122 had no sex reported. Of the 4,950 post-marketing primary dose cases, 4 cases reported information on variant sequencing; Alpha (1), B.1.617.2 lineage (1), Delta (1), and the remaining case reported coinfection with both Omicron and Delta variant. Three of these cases were not fatal, life-threatening, required hospitalisation or were disabling. However, the remaining case, reporting PCR-verified Alpha variant was fatal.

Cumulatively, 13,868 post-marketing (11,469 medically confirmed and 2,399 medically unconfirmed) primary dose cases reporting events of vaccine failure or LOE were identified. Of these 13,868 cases, 12,137 were serious and 1,731 were nonserious and reported a total of 24,579 EOI (21,864 serious, 2,715 nonserious).

Table 39: Time to Onset in Primary Dose Cases Involving the Use of Ad26.CoV2.S and Reporting Vaccine Failure, Lack of Efficacy/Effectiveness (Cases=4,950)

TTO	Number of Cases
≤14 days	43
>14 days but ≤28 days	26
>28 days	4,668
NA[a]	9
NR	204
Total[b]	**4,950**

Key: NA=Not Applicable; NR=Not Reported; PBRER=Periodic Benefit Risk Evaluation Report; TTO=Time to Onset

a: These cases reported foetal exposure during pregnancy; vaccine was not administered to neonate/infant.

b: TTO categories have been presented at the case level in the current PBRER, as compared to the event level presented in the previous PBRER.

The Company case definition of vaccination failure is as follows: medically confirmed, TTO >14 days, and positive COVID-19 testing; 4,530 of the 4,950 post-marketing primary dose cases met this case definition. Additionally, 38 of the 4,950 cases also reported suspected vaccination failure. In these 38 cases, TTO was greater than 14 days and were medically confirmed; however, no laboratory test results were specified.

Note that in the previous reporting period (25 August 2021 to 24 February 2022), the number of cases meeting criteria of vaccination failure/LOE was erroneously reported as 112 cases. The correct total was 3,110 cases. As all cases meeting search criteria received during the reporting interval were considered in the conclusions, there was no change to the benefit-risk analysis as a result of this error.

Figure 2: Case Count of Post-Marketing marketing Primary Dose Spontaneous Cases by Month Involving the Use of Ad26.COV2.S and Reporting Vaccine Failure, Lack of Efficacy/Effectiveness

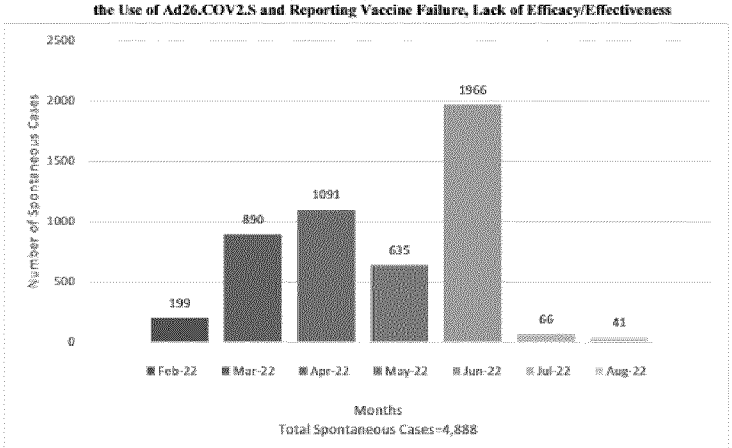

Table 41: Serious MedDRA PTs of Interest and Their Outcomes in Post-marketing, Primary Dose Cases Reporting Vaccine Failure, Lack of Efficacy/Effectiveness With the Use of Ad26.COV2.S (Events=9,138)

MedDRA PTs	Number of Event Outcomes						
	Fatal	Not Resolved	Resolved	Resolved With Sequelae	Resolving	NR	Total Number of Events[a]
Vaccination failure	4	4	10	0	10	4,494	4,522
COVID-19	19	10	25	0	8	4,364	4,426
SARS-CoV-2 test positive	15	9	21	1	4	10	60
Thrombosis with thrombocytopenia syndrome[b]	4	3	8	0	1	12	28
COVID-19 pneumonia	12	6	2	1	2	4	27
Suspected COVID-19	2	3	0	0	0	19	24
Drug ineffective	0	4	0	0	4	9	17
SARS-CoV-2 test negative	0	7	0	0	0	1	8

Key: COVID-19=Coronavirus Disease-2019; MedDRA=Medical Dictionary for Regulatory Activities; NR=Not Reported; PT=Preferred Term; SARS-CoV-2=Severe Acute Respiratory Syndrome Coronavirus-2

a: A single case may report more than 1 event of interest. The PTs having frequency ≥8 are presented.

b: Additional information included in Section 16.3.1.1, Thrombosis With Thrombocytopenia Syndrome.

Fatal Post-marketing Primary Dose Cases

During the reporting interval, 49 initial, fatal cases were reported. Of these 49 fatal cases, 21 met the case definition of confirmed vaccination failure and 6 met the case definition of suspected vaccination failure. Overall, 51 EOI were reported in these 27 fatal cases during the interval. Of these 27 cases, 16 concerned males, 10 females, and 1 had no sex reported. The age range was 40 to 94 years. Among patients where age was reported, 1 was in the age range of 36 to 50 years, 6 were in the age range of 51 to 64 years, and 20 were ≥65 years.

Booster dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 418 (113 medically confirmed and 305 medically unconfirmed) post-marketing cases reported as booster were identified. There were 249 serious cases and 169 nonserious cases and reported a total of 674 EOI20 (302 serious; 372 nonserious). Of these cases, 288 were heterologous and 130 were homologous. These 418 cases reported 302 serious EOI. Of these 418 cases, the most frequently reported country/territory of origin was the US (n=254). Of the 418 cases, 214 cases concerned females, 145 males, and 59 had no sex reported. The age range was 19 to 96 years. The EOI (≥107) included COVID-19 (n=226), vaccination failure (n=209), and suspected COVID-19 (n=107). Where reported (n=262), the outcomes were not resolved (n=103), resolved (n=88), resolving (n=65), fatal (n=5), and resolved with sequelae (n=1).

Cumulatively, 667 (225 medically confirmed and 442 medically unconfirmed) post-marketing cases reported as booster were identified. Of these cases, 375 cases were serious and 292 were nonserious and reported a total of 1,060 EOI20 (451 serious; 609 nonserious). Of these cases, 433 were heterologous and 234 were homologous.

Of the 418 post-marketing cases reported as booster, 1 case reported the presence of the Omicron variant. This was a fatal heterologous case concerning a 96-years-old female patient with atrial fibrillation, dyslipidaemia, stroke, arterial hypertension, senile macular degeneration, cardiac failure, and haemorrhage of digestive tract as concurrent conditions.

During the reporting interval, 6 fatal booster cases were reported. Of these 6 cases, 4 met the definition of confirmed vaccination failure (1 homologous and 3 heterologous). Of the 4 fatal confirmed vaccination failure cases, 3 concerned males and 1 female. The age range reported in these 4 cases was 68 to 96 years.

MAH Conclusion Based on the review of all the available data, no new significant safety information is observed in the review of vaccination failure cases. No signal suggestive of vaccine failure has been

identified with Ad26.COV2.S. The Company will continue to monitor and present cases of vaccination failure in upcoming PBRERs.

Rapporteur assessment comment:

During the PSUR interval, lack of efficacy was reported in 4,950 post-marketing primary dose cases, which is a small decrease from last PSUR which might reflect the decreased use of this vaccine in US and EEA countries. Only 4/4,950 cases reported information on variant sequencing.

In addition, 418 cases of vaccine failure when administered as a booster dose was reported post-marketing.

Very limited information on the SARS-CoV-2 variants have been provided. No new safety concern detected for this item.

Reactogenicity

During the interval reporting period of 25 February 2022 to 24 August 2022, 211 (64 medically confirmed and 147 medically unconfirmed) initial, primary dose cases reporting reactogenicity were identified. All of the cases were serious and reported a total of 702 serious EOI. All 211 primary dose cases received during the interval reporting period were reported from post-marketing sources (including spontaneous and solicited). No cases were reported from Janssen Sponsored Clinical Studies or Janssen Supported Clinical Studies.

Cumulatively, 1,465 (670 medically confirmed and 795 medically unconfirmed) primary dose cases reporting reactogenicity were identified. All of the cases were serious and reported a total of 3,495 serious EOI. Of the 1,465 cumulative primary dose cases received, 6 were reported from Janssen Sponsored Clinical Studies, 8 from Janssen Supported Clinical Studies, and 1,451 from post-marketing sources (including spontaneous and solicited cases).

Table 52: Frequency of MedDRA PTs of Interest in Post-marketing, Primary Dose Cases Reporting Local Reactogenicity Reactions With the Use of Ad26.COV2.S

MedDRA PTs	Number of Serious Events Received During Reporting Period[a]	Number of Serious Events Received Cumulatively
Injection site pain	53	127
Injection site swelling	9	27
Vaccination site pain	7	18
Vaccination site reaction	3	4
Injection site bruising	2	3
Injection site erythema	1	10

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: The MedDRA PTs of interest were sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022).

Table 54: Frequency of MedDRA PTs of Interest Reported in Post-marketing, Primary Cases Reporting Systemic Reactogenicity With the Use of Ad26.COV2.S

MedDRA PTs	Number of Serious Events Received During Reporting Period[a]	Number of Serious Events Received Cumulatively
Headache	119	565
Fatigue	107	368
Dizziness	76	369
Pyrexia	66	417
Myalgia	50	233
Arthralgia	35	143
Paraesthesia	34	153
Chills	30	241
Hypoaesthesia	24	156
Pain in extremity	20	164
Asthenia	19	150
Diarrhoea	18	83
Vomiting	17	131
Muscular weakness	12	71

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: The MedDRA PTs of interest were sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022).

Booster dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 29 (6 medically confirmed and 23 medically unconfirmed) initial cases reported as booster were identified. All of the cases were serious and reported a total of 69 serious EOI. Of these cases, 21 were heterologous and 8 were homologous.
All 29 primary dose cases received during the interval reporting period were reported from post-marketing sources (including spontaneous and solicited).
Cumulatively, 53 (15 medically confirmed and 38 medically unconfirmed) cases reported as booster were identified. All of the cases were serious and reported a total of 121 serious events. Of these cases, 32 were heterologous and 21 were homologous. Cumulatively, all 53 booster cases were reported from post-marketing sources (including spontaneous and solicited).

MAH Conclusion Local and systemic reactogenicity symptoms are included in the CCDS as common adverse
reactions. The review of the cases received during the reporting period have not shown any changes in terms of severity or outcome warranting changes to the prescribing information (PI). No signal of vaccination anxiety-related reactions has been identified with Ad26.COV2.S.

Rapporteur assessment comment:

The reported local and systemic reactions are in line with what is already included in the product information. No new safety concern is detected here.

2.2.3. Closed signals

Closed and Refuted Signals

During the reporting period, the following signals were closed but with continued routine pharmacovigilance.

IgA Nephropathy

Request: On 22 February 2022, the Company received a request from the WHO Uppsala Monitoring Centre:

"to comment on a safety signal for IgA nephropathy following administration of COVID-19 vaccines, which was detected during screening of the WHO safety database VigiBase on 21 April 2021. The health authorities mentioned that as of 31 October 2021, 64 cases reporting IgA nephropathy following COVID-19 vaccination underwent manual clinical evaluation. The majority of cases followed administration of an mRNA based COVID-19 vaccine. The WHO Uppsala Monitoring Center invited Janssen to comment on this signal by the date of 07March2022."

MAHs conclusion: Based on the review of evidence from cases from interventional clinical studies and post-marketing surveillance data, there is no evidence of an association between the event of IgA nephropathy and vaccination with Ad26.COV2. S. vaccine.

Additional information on this analysis can be found in Section 8, Overview of Signals, in the bimonthly Summary Safety Report dated 16 January 2022 to 15 March 2022.

Rapporteur assessment comment:

A cumulative review was executed in EMEA/H/C/005737/MEA/014.9 SSR, in which no evidence of causal association between the event of IgA nephropathy and vaccination with JCovden was detected.

Facial Paralysis

Request: During the generation of the previous PBRER dated 25 August 2021 to 24 February 2022, a pooled analysis of the double-blind phases of 5 Company-sponsored trials showed a numerical imbalance for facial paralysis between Ad26.COV2.S and placebo. An analysis was conducted on all available data.

MAHs conclusion: Overall, these data support a revision to the Ad26.COV2.S Product Information to include facial paralysis (including Bell's palsy) with a frequency of"rare". The Company added facial paralysis including Bell's Palsy as an ADR. The Company will continue to monitor cases of facial paralysis (including Bell's palsy) through routine pharmacovigilance activities.

Additional information can be found in Section 2.1 of the Response document titled: Response to the PRAC Rapporteur's Preliminary Assessment Report: Periodic Safety Update Report (Reporting Period: 25 August 2021 to 24 February 2022) JCOVDEN Procedure Number: EMEA/H/C/PSUSA/00010916/202202 (dated 26 August 2022). PRAC has endorsed the Company's updates.

Rapporteur assessment comment:

With the last PSUR it was decided to include facial paralysis with the frequency "rare" in the SmPC, section 4.8.

Coronary Artery Disease, including Myocardial Infarction

Request: On 08 March 2022, the Company received the PRAC FAR for the ninth SSR, which requested a legally binding measure (LEG) for Ad26.COV2.S to include an in-depth review of CAD including AMI; a discussion of the French EPI-PHARE epidemiological study that indicated a slight increased risk of myocardial infarction (MI) in the first 2 weeks following vaccination with Ad26.COV2.S; and a cumulative review of CAD (including AMI) cases, based on data from clinical trials, post-marketing data and literature, including (age) stratified O/E analyses.

MAHs conclusion: Based on review of all available data, the weight of cumulative evidence is insufficient to support a causal association between CAD (including AMI) and the Ad26.COV2.S vaccine.

Key factors supporting this conclusion include lack of established biological plausibility, no increased risk observed from review of a large clinical trial dataset, and insufficient evidence from the biomedical literature, clinical trials, and aggregate post-marketing spontaneous reports as well as RWE to support a causal relationship between the development of CAD (including AMI) and Ad26.COV2.S. The Company will continue to monitor events of CAD (including AMI) via routine PV activities.

Rapporteur assessment comment:

An in-depth analysis on myocardial infarction in the first 2 weeks following vaccination was performed. No causal association was established, and the signal was closed which is endorsed. The MAH has presented an update on the analysis of cardiac disorders including MI in the AESI section below.

Closed Signals That are Categorised as Important Identified Risks

Venous Thromboembolism

Request: During the reporting period of the bimonthly SSR (16 March 2022 to 15 May 2022), the Company conducted an updated review of VTE.

Conclusion: After the review of the data from different sources (pooled safety data from clinical trials, literature, O/E, real world data [RWD] analysis and post-marking reporting), the Company considered that there is sufficient evidence of a causal relationship between Ad26.COV.2.S vaccination and the occurrence of venous thromboembolism. Consequently, the CCDS and the cRMP will be updated to add venous thromboembolism as an ADR and an important identified risk respectively.

Additional information on this analysis can be found in Section 8.4, Overview of Signals in the bimonthly SSR dated 16 March 2022 to 15 May 2022 and in Section 16.3.1.3, Venous thromboembolism below.

Venous thromboembolism has been reclassified as an important identified risk in the EU RMP. The cRMP is in the process of being updated to reflect the reclassification.

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). There is no additional new safety concern detected with VTE.

Closed Signals That are Categorised as Important Potential Risks

There were no closed signals were categorised as important potential risks.

Closed Signals That are Identified Risks not Categorised as Important

There were no closed signals that were categorised as identified risks not categorised as important.

Closed Signals That are Potential Risks not Categorised as Important

There were no closed signals that were categorised as potential risks not categorised as important.

2.3. Evaluation of risks and safety topics under monitoring

Effectiveness of Targeted Follow-up Questionnaires

In alignment with EU GVP Module V, the Company has implemented specific follow-up questionnaires for certain events of special interest as part of its routine pharmacovigilance activities. During the reporting period, the following Targeted Follow-up Questionnaires (TFUQs) were used by the Company for Ad26.COV2.S post-marketing surveillance:

Safety Concern/Event of Interest	Purpose/Description
Thrombosis with thrombocytopenia syndrome Venous thromboembolism	TFUQ for the characterization of venous thromboembolism and thrombosis with thrombocytopenia syndrome.
Vaccine-associated enhanced disease, including VAERD	TFUQ to collect information on vaccination failure/lack of effect, including events of VAED and VAERD.
Multisystemic Inflammatory Syndrome	TFUQ to collect information on MIS in Adults (MIS-C). Currently the Company has no paediatric indication for Ad26.COV2.S.

Key: MIS=Multisystemic Inflammatory Syndrome; TFUQ=Targeted Follow-up Questionnaires; VAED=Vaccine-associated Enhanced Disease; VAERD=Vaccine-associated Enhanced Respiratory Disease

Results

During the reporting period, the Company issued at least 1 TFUQ for 247 cases in the US, of which 47 had a reply received by the Company. Cumulatively since launch, the Company has issued at least 1 TFUQ for 2,062 cases in the US, of which 231 had a reply received by the Company (this includes questionnaires for the topic of Anaphylaxis, no longer followed up using TFUQ).

In the EEA and Rest of World (ROW), the issuing of TFUQs is carried out by each Local Operating Company; therefore, the Company has no centralised process for the collection of issued/answered TFUQs.

Conclusion

Overall, response rates from targeted questionnaires have been consistently low. This is in line with the general experience from the Company in the issuing of TFUQs.

Given the very low usage of the vaccine in both the US and EEA, in addition to the relatively low response rates, the Company proposes the retirement of the 3 currently active TFUQs, and to continue to monitor the conditions of interest through their associated PV activities (for TTS/VTE and VAED/VAERD) and routine PV activities (MIS).

PRAC Rapporteur comments: retiring these FUQ is endorsed. The RMP can be updated at the next regulatory opportunity.

New Information on Important Identified Risks

Anaphylaxis has been removed from both the cRMP (version 5.0) and from the EU RMP (version 4.2).

Thrombosis With Thrombocytopenia Syndrome

According to the cRMP (version 4.0; dated 09 December 2021), TTS is an important identified risk associated with the use of Ad26.COV2.S.

Primary Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 38 (33 medically confirmed and 5 medically unconfirmed) initial, primary dose cases reporting TTS were identified. All 38 cases were serious and reported a total of 113 EOI (111 serious; 2 nonserious). Of these 38 primary dose cases received during the interval reporting period, 4 were reported from Janssen Sponsored Clinical Studies and 34 from post-marketing sources (including spontaneous and solicited). No cases were reported from Janssen Supported Clinical Studies. Cumulatively, 236 (192 medically confirmed and 44 medically unconfirmed) primary dose cases reporting TTS were identified. Of these cases, 235 were serious and 1 nonserious and reported a total of 1,023 EOI (1,009 serious; 14 nonserious).

Of the 236 cumulative primary dose cases received, 7 were reported from Janssen Sponsored Clinical Studies, 2 from Janssen Supported Clinical Studies, and 227 from post-marketing sources (including spontaneous and solicited cases).

Janssen Sponsored Clinical Studies Primary Dose Cases

During the reporting period, 4 initial, primary dose cases were retrieved from Janssen Sponsored Clinical Studies. All 4 cases were reported from VAC31518COV3001. These 4 cases reported 8 EOI (6 serious; 2 nonserious). Of these 4 cases, the reported countries/territories of origin were the US (n=3), followed by Brazil (n=1). These cases concerned 3 males and 1 female. The age range was from 47 to 72 years. The EOI included thrombocytopenia (n=3), deep vein thrombosis (n=2), and transient ischaemic attack, myocardial infarction, and platelet count decreased (n= 1 each). The mean and median TTO was 380.1 days and 369.5 days, respectively. The outcome of the 8 EOI was reported as resolved (n=6), resolving (n=1), and resolved with sequelae (n=1).

Post-marketing Sources (Including Spontaneous and Solicited) Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 34 post-marketing sources (including spontaneous and solicited), initial, primary dose cases reporting TTS were identified. These 34 ost-marketing, primary dose cases reported 105 serious EOI.

Cumulatively, 227 (183 medically confirmed and 44 medically unconfirmed) post-marketing,primary dose cases reporting TTS were identified. Of these cases, 226 were serious and 1 was nonserious and reported a total of 1,004 EOI (994 serious; 10 nonserious).

During the reporting period, of the 34 post-marketing, initial, primary dose cases, the most frequently reported countries/territories of origin (n≥4) were Germany (n=14), followed by the US (n=8) and Italy (n=4). These cases concerned 15 males, 11 females, and 8 did not report sex. The age range was from 20 to 70 years.

Table 64: Frequency of MedDRA PTs of Interest in Post-marketing, Primary Dose Cases Reporting Thrombosis with Thrombocytopenia Syndrome With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Thrombosis with thrombocytopenia syndrome	25	0	57	0
Cerebral venous sinus thrombosis	13	0	67	0
Pulmonary embolism	10	0	100	0
Deep vein thrombosis	9	0	59	0
Thrombocytopenia	6	0	129	0
Cerebrovascular accident	4	0	21	0
Platelet count decreased	3	0	99	7
Cerebral venous thrombosis	3	0	16	0
Embolism	2	0	4	0
Venous thrombosis	2	0	9	0
Portal vein thrombosis	2	0	20	0
Coronary artery thrombosis	2	0	4	0
Aortic thrombosis	2	0	10	0
Immune thrombocytopenia	2	0	19	0
Jugular vein thrombosis	2	0	17	0

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: The MedDRA PTs of interest with frequency ≥2 have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event of interest.

For the reporting period, the EOI (n≥3) included thrombosis with thrombocytopenia syndrome (n=25), cerebral venous sinus thrombosis (n=13), pulmonary embolism (n=10), deep vein thrombosis (n=9), thrombocytopenia (n=6), cerebrovascular accident (n=4), and platelet count decreased and cerebral venous thrombosis (n=3 each). The mean and median TTO were 36.4 days and 14 days respectively. Where reported (n=50), the outcomes were not resolved (n=17), resolved (n=14), fatal (n=12), resolving (n=4), and resolved with sequelae (n=3).

In addition, for the reporting period, the Company has stratified these 34 post-marketing, initial, primary dose cases by age group and sex and applied the TTS working case definitions from Brighton Collaboration (BC), CDC, and PRAC (see Table 65).

Table 65: Number of Cases by Age and Sex and Working Case Definitions for Post-marketing Cases Reporting Thrombosis With Thrombocytopenia With the Use of Ad26. COV2.S Vaccine for the Reporting Period (Cases=34; Events=105)

Age Group (Years)	18 to 35		36 to 50			51 to 64		≥65		NR	
Sex	F	M	F	M	NR	F	M	F	M	F	NR
CDC											
Tier 1	0	1	2	1	2	0	1	0	0	0	0
Tier 2	0	0	0	0	0	0	0	0	0	0	0
Neither	1	2	1	6	0	5	3	1	1	1	6
Total	**1**	**3**	**3**	**7**	**2**	**5**	**4**	**1**	**1**	**1**	**6**
Brighton Collaboration											
Level 1	0	1	2	2	0	2	2	0	0	1	0
Level 2	0	0	0	0	0	0	0	0	0	0	0
Level 3	0	0	0	0	2	0	0	0	0	0	0
Level 4	1	2	0	5	0	3	0	1	0	0	6
Level 5	0	0	1	0	0	0	2	0	1	0	0
Total	**1**	**3**	**3**	**7**	**2**	**5**	**4**	**1**	**1**	**1**	**6**
PRAC											
Confirmed	0	0	1	1	0	0	0	0	0	0	1
Probable	1	0	0	1	0	1	0	0	0	0	0
Possible	0	2	1	3	2	4	3	1	0	1	1
Unlikely	0	0	1	0	0	0	1	0	1	0	0
Criteria not met	0	1	0	2	0	0	0	0	0	0	4
Total	**1**	**3**	**3**	**7**	**2**	**5**	**4**	**1**	**1**	**1**	**6**

Key: CDC=Centers for Disease Control and Prevention; F=Female; M=Male; NR=Not Reported; PRAC=Pharmacovigilance Risk Assessment Committee

Fatal Post-marketing Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 8 post-marketing, initial, primary dose fatal cases with 12 fatal EOIs were retrieved. Of the 8 fatal cases, 3 concerned males, 2 females, and 3 did not report sex. The age range was 37 to 66 years. There were 4 patients in the age range of 36 to 50 years, 1 patient in the age ≥65 years, and the age was not reported in 3 cases.

The mean and median TTO reported in these 12 fatal EOI were 72.5 days and 66 days, respectively. The fatal EOI were thrombosis with thrombocytopenia syndrome (n=4) and portal vein thrombosis, brain stem stroke, cerebrovascular accident, thrombocytopenia, embolism, venous thrombosis, immune thrombocytopenia, and myocardial infarction (n=1 each).

Booster Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 4 (all medically confirmed) initial cases reported as booster were identified. All cases were serious and reported a total of 7 serious EOI. All 4 cases were heterologous and were reported from post-marketing sources (non-interventional solicited clinical study). No cases were reported from Janssen Sponsored Clinical Studies or Janssen Supported Clinical Studies.

Cumulatively, 5 (all medically confirmed) cases reported as booster were identified. All cases were serious and reported a total of 13 serious EOI. All 5 cases were heterologous. All 5 cumulative cases reported as booster were reported from post-marketing sources (including spontaneous and solicited cases). No cases were reported from Janssen Sponsored Clinical Studies or Janssen Supported Clinical Studies. Cumulatively, 1 medically confirmed, serious, heterologous, post-marketing case was identified reporting CVST and thrombocytopenia in a 48-year-old male who received a primary vaccination with an mRNA vaccine followed by a booster dose of Ad26.COV2.S 208 days later. The event of CVST occurred approximately 8 months after the primary mRNA vaccination and 12 days after the booster dose with Ad26.COV2.S. The patient had a history of hypertension and dyslipidaemia. The case was assessed as BC level 1, CDC Tier 1, and PRAC "possible". The outcome was fatal (unspecified). It was unknown whether autopsy was performed. No new information has been received since the last interval.

There were no fatal cases reported as booster which were retrieved from the search of the Company global safety database during the interval reporting period of 25 February 2022 to 24 August 2022.

Literature ICSR

No information was identified that would change the characterisation of risk.

MAH Conclusion

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

Rapporteur assessment comment
TTS is included in section 4.4 & 4.8 of the SmPC (and the PIL accordingly). It has been furthermore evaluated in a signal with EPITT 19689; EMEA/H/C/005737/II/0006/G; and in the MSSRs EMEA/H/C/005737/MEA/014.1 – 07. No additional new safety concern has occurred for TTS during the current reporting interval.

Guillain-Barré Syndrome

According to the cRMP (version 4.0; dated 09 December 2021), GBS is an important identified risk associated with the use of Ad26.COV2.S.

Primary Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 72 (30 medically confirmed and 42 medically unconfirmed) initial, primary dose cases reporting GBS were identified. All these cases were serious and reported a total of 76 serious EOI.

Of these 72 primary dose cases received during the interval reporting period, 1 was reported from a Janssen Sponsored Clinical Study and 71 from post-marketing sources (including spontaneous and solicited). No cases were reported from Janssen Supported Clinical Studies.

Cumulatively, 593 (343 medically confirmed and 250 medically unconfirmed) primary dose cases reporting GBS were identified. Of these 593 cases, 592 were serious and 1 was nonserious and reported a total of 626 EOI (625 serious; 1 nonserious).

Of the 593 cumulative primary dose cases received, 9 were reported from Janssen Sponsored Clinical Studies, 2 from Janssen Supported Clinical Studies, and 582 from post-marketing sources (including spontaneous and solicited cases).

Janssen Sponsored Clinical Studies Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 1 initial, primary dose case reporting GBS was retrieved from a Janssen Sponsored Clinical Study. This serious case was from VAC31518COV3009 and concerned a 61-year-old female from [redacted] This case reported a serious EOI of GBS with TTO of 466 days. The outcome for the EOI was reported as resolving.

Post-marketing Sources (Including Spontaneous and Solicited) Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 71 post-marketing sources (including spontaneous and solicited), initial, primary dose cases reporting GBS were retrieved. These 71 post-marketing, initial, primary dose cases reported 75 serious EOI. Cumulatively, 582 (332 medically confirmed and 250 medically unconfirmed) post-marketing, primary dose cases reporting GBS were identified. All these cases were serious and reported a total of 615 serious EOI.

Of these 71 post-marketing, initial, primary dose cases, the most frequently reported countries/territories of origin (n≥18) were the US (n=24) and Germany (n=18). These cases concerned 39 males, 28 females, and 4 did not report sex. The age range was from 18 to 87 years. The frequency distribution of the MedDRA PTs of interest reported in post-marketing, primary dose cases is presented in Table 67 below. A single case may contain more than 1 EOI.

Table 67: Frequency of MedDRA PTs of Interest in Post-marketing, Primary Dose Cases Reporting GBS With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Guillain-Barre syndrome	62	0	529	0
Chronic inflammatory demyelinating polyradiculoneuropathy	8	0	37	0
Demyelinating polyneuropathy	2	0	17	0
Miller Fisher syndrome	2	0	19	0
Acute motor axonal neuropathy	1	0	2	0

Key: GBS=Guillain-Barré Syndrome; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term

a: The MedDRA PTs of interest have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event of interest.

The most frequently reported EOI (n≥8) was GBS (n=62) and chronic inflammatory demyelinating polyradiculoneuropathy (n=8). The mean and median TTO were 52.8 and 15 days, respectively. Where reported (n=60), the outcome was not resolved (n=33), resolving (n=19), resolved with sequelae (n=5), resolved (n=2), and fatal (n=1).

Fatal Post-marketing Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 1 post-marketing, initial, primary dose case with 1 fatal EOI was retrieved. The fatal EOI was GBS. This fatal case concerned a 79-year-old female with concurrent conditions of hypertensive cardiomyopathy and GBS who experienced an exacerbation of GBS approximately 276 days following vaccination with Ad26.COV2.S. It was unknown if an autopsy was reported.

Booster Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 8 (no medically confirmed and 8 medically unconfirmed) initial cases reported as booster were identified. All cases were serious and reported a total of 8 serious EOI. Of these cases, 5 were heterologous and 3 were homologous. All 8 booster cases reported as booster during the interval were reported from post-marketing sources (including spontaneous and solicited). No cases were reported from Janssen Sponsored Clinical Studies or Janssen Supported Clinical Studies.

Cumulatively, 10 (1 medically confirmed and 9 medically unconfirmed) cases reported as booster were identified. All cases were serious and reported a total of 10 serious EOI. Of these cases, 7 were heterologous and 3 were homologous. All 10 cumulative cases reported as booster were reported from post-marketing sources (including spontaneous and solicited cases). No cases were reported from Janssen Sponsored Clinical Studies or Janssen Supported Clinical Studies.

Post-marketing Sources (Including Spontaneous and Solicited) Booster Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 8 post-marketing sources (including spontaneous and solicited),initial cases reported as booster were retrieved. These 8 post-marketing, booster dose cases reported 8 serious EOI.

Cumulatively, 10 (1 medically confirmed and 9 medically unconfirmed) post-marketing cases reported as booster were identified. All cases were serious and reported a total of 10 serious EOI.

An overview of these post-marketing, booster dose cases is presented in Table 68 below.

Table 68: Characteristics of Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting GBS

Case Characteristics		Number of Cases Received During the Interval Reporting Period=8	Number of Cases Received Cumulatively=10
Sex	Male	6	6
	Female	2	3
	NR	0	1
Age (Years)[a]	18 to 35	1	1
Minimum: 24	36 to 50	1	2
Maximum: 76	51 to 64	4	4
Mean: 54.9	≥65	2	2
Median: 57.5	NR	0	1
Country/Territory[b]	Brazil	2	3
	Germany	2	2
	Netherlands	1	1
	Philippines	1	1
	South Africa	1	1
	United States	1	2
Sources	Spontaneous	8	10
Classification	Heterologous	5	7
	Homologous	3	3
Event Characteristics		**Number of Events=8**	**Number of Events=10**
Seriousness (Event Level)[c]	Serious	8	10
Outcome (Event Level)[c]	Not resolved	3	3
	Fatal	1	1
	Resolved	1	1
	Resolving	1	1
	NR	2	4

Key: GBS=Guillain-Barré Syndrome; NR=Not Reported

a: The calculation was based on the current reporting period (25 February 2022 to 24 August 2022).

b: Countries/Territories were presented in decreasing order for the current reporting period (25 February 2022 to 24 August 2022).

c: Seriousness and outcome have been presented for the events of interest.

Of these 8 post-marketing, initial cases reported as booster, the most frequently reported countries/territories of origin (n≥2) were Brazil and Germany (n=2 each). These cases concerned 6 males and 2 females. The age range was from 24 to 76 years. The frequency distribution of the MedDRA PTs of interest reported in post-marketing cases reported as booster is presented in Table 69 below.

Table 69: Frequency of MedDRA PTs of Interest in Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting GBS

MedDRA PTs	Number of Events Reported During the Interval Reporting Period		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Guillain-Barre syndrome	8	0	10	0

Key: GBS=Guillain-Barré Syndrome; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term

The EOI reported was Guillain-Barre Syndrome (n=8). The mean and median TTO were 132.8 and

100 days, respectively. Where reported (n=6), the outcome was not resolved (n=3), fatal (n=1), resolved (n=1), and resolving (n=1).

Fatal Post-marketing Booster Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 1 initial, case reported as booster with 1 fatal EOI was retrieved. This case from South Africa concerned a 37-year-old male who experienced GBS, slurred speech, inability to walk, and tingling in feet/hands approximately 2 days following a booster dose of Ad26.COV2.S. An unspecified duration later, following booster vaccination, the patient died from GBS. It was unspecified whether an autopsy was performed. No additional details were

provided including relevant medical history/concurrent conditions, clinical course/treatment, and supporting diagnostic data.

Literature ICSR

No new or significant information identified which changed the characterisation of this risk.

MAH Conclusion

Based on the evaluation of the cases, and review of safety from other sources, the information is consistent with the information known about GBS. The Company will continue to closely monitor GBS as an important identified risk

Rapporteur assessment comment
GBS has been included in section 4.4 and 4.8 of the SmPC in the frame of procedure EMEA/H/C/005737/II/0012. No additional new safety concern is detected here.

Venous Thromboembolism

Venous thromboembolism has been reclassified as an important identified risk in the EU RMP. The cRMP is in the process of being updated to reflect the reclassification. According to the cRMP (version 4.0; dated 09 December 2021), VTE is an important potential risk associated with the use of Ad26.COV2.S. However, on 10 May 2022, based on the evidence from post-marketing data sources, the Company upgraded VTE from an important potential to an important identified risk. The cRMP is in the process of being updated to reflect this change.

Primary Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 559 (317 medically confirmed and 242 medically unconfirmed), initial, primary dose cases reporting VTE were identified. Of these 559 cases, 522 were serious and 37 were nonserious and reported a total of 740 EOI (686 serious, 54 nonserious).

Of these 559 primary dose cases received during the interval reporting period, 63 were reported from Janssen Sponsored Clinical Studies, 1 from a Janssen Supported Clinical Study, and 495 from post-marketing sources (including spontaneous and solicited). Cumulatively, 4,693 (2,862 medically confirmed and 1,831 medically unconfirmed) primary dose cases reporting VTE were identified. Of these cases, 4,539 cases were serious and 154 were nonserious and reported a total of 6,460 EOI (6,201 serious; 259 nonserious).

Of the 4,693 cumulative primary dose cases received, 218 were reported from Janssen Sponsored Clinical Studies, 44 from Janssen Supported Clinical Studies, and 4,431 from post-marketing sources (including spontaneous and solicited cases).

Janssen Sponsored Clinical Studies Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 63 initial, primary dose cases reporting VTE were retrieved from Janssen Sponsored Clinical Studies. Of the 63 cases, 37 were from VAC31518COV3001, 23 from VAC31518COV3009, 2 from VAC31518COV1001, and 1 from VAC31518COV3005. These 63 cases reported 69 EOI (49 serious, 20 nonserious). Of these 63 cases, the most frequently reported countries/territories of origin (n≥9) were the US (n=25), followed by Brazil

(n=10) and South Africa (n=9). These cases concerned 37 males and 26 females. The age range was from 27 to 84 years.

Upon case level review, it has been determined that 6 patients were administered placebo. These cases ([redacted] and [redacted]) are in the process of being updated and the change will be reflected in the next scheduled PBRER.

The most frequently reported EOI (n≥4) included deep vein thrombosis (n=22), pulmonary embolism (n=17), cerebrovascular accident (n=9), and cerebral infarction and venous thrombosis limb (n=4 each). The mean and median TTO were 393.8 and 388.5 days, respectively. Where reported (n=67), the outcomes were resolved (n=28), resolving (n=25), not resolved (n=8), resolved with sequelae (n=5), and fatal (n=1).

Janssen Supported Clinical Studies Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 1 initial, primary dose case reporting VTE was retrieved from a Janssen Supported Clinical Study. The case was from VAC31518COV3021 and concerned an 84-year-old male from South Africa reporting a serious EOI of cerebellar infarction. The TTO was 6 days. The outcome for the EOI was reported as resolving.

Post-marketing Sources (Including Spontaneous and Solicited) Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 495 post-marketing sources (including spontaneous and solicited), initial, primary dose cases reporting VTE were retrieved. These 495 post-marketing, initial, primary dose cases reported 670 EOI (636 serious; 34 nonserious).

Cumulatively, 4,431 (2,600 medically confirmed and 1,831 medically unconfirmed) post-marketing, primary dose cases reporting VTE were identified. Of these cases, 4,328 were serious and 103 were nonserious and reported a total of 6,171 EOI (5,979 serious; 192 nonserious).

Of these 495 post-marketing, initial, primary dose cases, the most frequently reported countries/territories of origin (n≥40) were the US (n=242), followed by Germany (n=72) and Poland (n=40). These cases concerned 225 males, 209 females, and 61 did not report sex. The age range was from 0.25 to 95 years.

The frequency distribution of the MedDRA PTs of interest reported in post-marketing, primary dose cases is presented in Table 71 below. A single case may contain more than 1 EOI.

Table 71: Frequency of MedDRA PTs of Interest in Post-marketing, Primary Dose Cases Reporting VTE With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Thrombosis	133	0	1,314	0
Pulmonary embolism	79	0	938	1
Deep vein thrombosis	65	0	782	1
Cerebrovascular accident	62	0	619	0
Thrombosis with thrombocytopenia syndrome	28	0	73	0
Cerebral venous sinus thrombosis	24	0	142	0
Hemiparesis	23	0	177	0
Ultrasound Doppler abnormal	14	6	209	49

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term; VTE=Venous Thromboembolism

a: The MedDRA PTs of interest with a frequency ≥20 have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event of interest.

The most frequent EOI (n≥20) included thrombosis (n=133), pulmonary embolism (n=79), deep vein thrombosis (n=65), cerebrovascular accident (n=62), thrombosis with thrombocytopenia syndrome (n=28), cerebral venous sinus thrombosis (n=24), hemiparesis (n=23), and ultrasound Doppler abnormal (n=20). The mean and median TTO were 90.6 and 37.0 days, respectively. Where reported (n=435), the outcomes were not resolved (n=217), resolved (n=89), resolving (n=67), fatal (n=41), and resolved with sequelae (n=21).

Fatal Post-marketing Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 44 post-marketing, initial, primary dose fatal cases were retrieved. Of these 44 cases, 32 reported fatal EOI (n=41). The fatal EOI were pulmonary embolism and thrombosis (n=8 each), cerebrovascular accident (n=6), central venous catheterisation and thrombosis with thrombocytopenia syndrome (n=4 each), cerebral thrombosis and hemiparesis (n=2 each), and brain stem stroke, cerebrovascular disorder, deep vein thrombosis, embolism, portal vein thrombosis, superficial vein thrombosis, and venous thrombosis (n=1 each). The mean and median TTO for the fatal EOIs (where onset dates were available) were 130.2 days and 117 days, respectively. Of the 32 cases reporting fatal EOI, 20 concerned males, 8 females, and 4 had no sex reported. The age range was 35 to 95 years, with mean and median of 62.8 and 64.5 years, respectively. Among patients where age was reported (28/32), 1 was in the age range of 18 to 35 years, 5 were in the age range of 36 to 50 years, 8 were in the age range of 51 to 64 years, and 14 were ≥65 years. Six of the 32 cases co-reported thrombocytopenia.

Booster Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 69 (34 medically confirmed and 35 medically unconfirmed) initial cases reported as booster were identified. There were 64 serious and 5 nonserious cases and reported a total of 93 EOI (85 serious; 8 nonserious). Of these cases, 34 were heterologous and 35 were homologous.

Of these 69 cases reported as booster during the interval, 6 were reported from Janssen Sponsored Clinical Studies and 63 from post-marketing sources (including spontaneous and solicited). No cases were reported from Janssen Supported Clinical Studies. Cumulatively, 135 (68 medically confirmed and 67 medically unconfirmed) cases reported as booster were identified. Of these cases, 129 cases were serious and 6 were nonserious and reported a total of 177 EOI (168 serious; 9 nonserious). Of these cases, 46 were heterologous and 89 were homologous.

Of the 135 cumulative cases reported as booster, 9 were reported from Janssen Sponsored Clinical Studies and 126 from post-marketing sources (including spontaneous and solicited cases). No cases were reported from Janssen Supported Clinical Studies.

Janssen Sponsored Clinical Studies Booster Dose Cases

During the interval reporting period of 25 February 2022 to 24 August 2022, 6 initial cases reported as booster were retrieved from Janssen Sponsored Clinical Studies. All 6 cases were from VAC31518COV3001 and VAC31518COV3009 (n=3 each). These 6 cases reported 6 EOI (2 serious; 4 nonserious). Of these 6 cases, the most frequently reported country/territory of origin (n≥2) was the US (n=2). These cases concerned 4 females and 2 males. The age range was from 45 to 65 years.

The EOI included deep vein thrombosis and pulmonary embolism (n=2 each), and cerebrovascular accident and venous thrombosis limb (n=1 each). The mean and median TTO were 282.8 and 231.5 days, respectively. The outcome for all EOI was either not resolved or resolving (n=3 each).

Post-marketing Sources (Including Spontaneous and Solicited) Booster Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 63 post-marketing sources (including spontaneous and solicited), initial cases reported as booster were retrieved. These 63 post-marketing booster dose cases reported 87 EOI (83 serious; 4 nonserious). Cumulatively, 126 (59 medically confirmed and 67 medically unconfirmed) post-marketing, cases reported as booster were identified. Of these cases, 125 cases were serious and 1 was nonserious and reported a total of 168 EOI (164 serious; 4 nonserious).

Of these 63 post-marketing, initial cases reported as booster, the most frequently reported countries/territories of origin (n≥11) were the US (n=28), followed by Germany (n=14) and Brazil (n=11). These cases concerned 36 males and 27 females. The age range was from 17 to 93 years.

The frequency distribution of the MedDRA PTs of interest reported in post-marketing cases reported as booster is presented in Table 73 below. A single case may contain more than 1 EOI.

Table 73: Frequency of MedDRA PTs of Interest in Post-Marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting VTE

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Thrombosis	16	0	37	0
Deep vein thrombosis	15	0	26	0
Pulmonary embolism	11	0	20	0
Ultrasound Doppler abnormal	5	1	8	1
Thrombosis with thrombocytopenia syndrome	4	0	4	0
Cerebral infarction	3	0	6	0
Cerebral thrombosis	2	0	3	0
Cerebral venous sinus thrombosis	2	0	3	0
Cerebrovascular accident	2	0	16	0
Hemiparesis	2	0	3	0
Monoplegia	2	0	2	0
Pulmonary thrombosis	2	0	8	0
Thrombectomy	2	0	2	0

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term; VTE=Venous Thromboembolism

a: The MedDRA PTs of interest with a frequency ≥2 have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event of interest.

The most frequent EOI (n≥10) included thrombosis (n=16), deep vein thrombosis (n=15), and pulmonary embolism (n=11). The mean and median TTO were 109.2 and 80.0 days, respectively. Where reported (n=64), the outcomes were not resolved (n=33), resolved (n=16), resolving (n=7), resolved with sequelae (n=6), and fatal (n=2).

Fatal Post-marketing Booster Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 3 initial, fatal cases reported as booster were retrieved. Of these 3 cases, 2 reported a fatal EOI (n=2). The fatal EOI was thrombosis (n=2). In both cases, the EOI occurred after the mRNA booster vaccine was administered at 9 days after the booster dose in 1 case while in the other case latency was unspecified.

Literature ICSR

There was a total of 39 ICSR literature cases (35 cases involving primary dose administration [including 13 cases with multiple unidentifiable patients] and 4 cases reported as the booster dose) received during the reporting period of 25 February 2022 to 24 August 2022. Of the 39 literature cases, 25 cases reported TTS. No information was identified that would change the characterisation of risk.

Recategorization of the Risk

In May 2022, based on sufficient converging evidence observed in the post-marketing setting, the Company made a decision to upgrade VTE from an important potential risk to an important identified risk. VTE was added as an adverse reaction to the CCDS based on the following:

- The presence of cases in close temporal association with no clear confounders in the Company global safety database.
- The O/E ratio was statistically significant above 1 (LB of 95% CI: >1) for Deep vein thrombosis and Pulmonary embolism in the restricted sensitivity analysis (18 to 59 years of age group).
- RWE rapid cycle analysis showed that the risk of VTE after the first Ad26.COV2.S dose in the 1 to 28 day risk window (the specified time window of concern for VTE) was increased ~1.25 times.
- Literature search identified an increase in frequency/RR/OR in individuals vaccinated with chimpanzee adenovector-based COVID-19 vaccines (other than Ad26.COV2.S) compared to mRNA/background rates.

MAH Conclusion

Based on the evaluation of the cases, and review of safety from other sources, the information is consistent with the information known about VTE. Since the Company changed the risk from potential to important in May 2022, the Company will continue to closely monitor VTE as an important identified risk.

Rapporteur assessment comment

Thromboembolism has been earlier in depth investigated in 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). There is no additional new safety concern detected with VTE.

New Information on Important Potential Risks

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

Introduction

According to the cRMP (version 4.0; dated 09 December 2021), vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD), is an important potential risk associated with the use of Ad26.COV2.S.

Primary Dose

There were no initial, primary dose cases retrieved from the search of the Company global safety database during the reporting period of 25 February 2022 to 24 August 2022. Cumulatively, 1 medically confirmed, serious, primary dose case reporting VAED, including VAERD, was identified. This case reported a total of 1 serious EOI of VAED from a post-marketing spontaneous source. The outcome was not reported for this EOI.

Booster Dose

There were no initial cases reported as booster, which were retrieved from the search of the Company global safety database during the interval reporting period of 25 February 2022 to 24 August 2022. In addition, cumulatively, there were no cases reported as booster.

Literature ICSR

No ICSR literature cases were received during the reporting period of 25 February 2022 to 24 August 2022.

MAH Conclusion

Based on the review of the literature (ie, Section 11), ongoing/completed clinical studies (ie, Sections 7, 8, and 9), and single case retrieved cumulatively from the Company global safety database, no new significant safety information was identified for the important potential risk of VAED, including VAERD.

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

Immune Thrombocytopenia

According to the cRMP (version 4.0; dated 09 December 2021), ITP is an important potential risk associated with the use of Ad26.COV2.S. In the EU RMP (version 2.5, dated 13 January 2022), this risk is characterised as "Thrombocytopenia, including ITP" and is listed as an important identified risk.

Primary Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 302 initial, primary dose cases reporting ITP were retrieved. Out of 302 cases, 30 (14 medically confirmed and 16 medically unconfirmed) cases were identified from post-marketing sources (including spontaneous and solicited) to meet the ASH case definition for ITP.

Cumulatively, 417 (304 medically confirmed and 113 medically unconfirmed) primary dose cases reporting ITP per ASH case definitions are presented. Of these cases, 305 were serious and 112 were nonserious and reported a total of 478 EOI (355 serious; 123 nonserious).

Of the 417 cumulative primary dose cases, 14 were reported from Janssen Sponsored Clinical Studies, 3 from Janssen Supported Clinical Studies, and 400 from post-marketing sources (including spontaneous and solicited cases).

Post-marketing Sources (Including Spontaneous and Solicited) Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 30 post-marketing sources (including spontaneous and solicited), initial, primary dose cases reporting ITP per ASH case definitions are presented. Of these 30 cases, 27 were serious and 3 were nonserious and reported a total of 37 EOI (32 serious; 5 nonserious).

Cumulatively, 400 (287 medically confirmed and 113 medically unconfirmed) post-marketing, primary dose cases reporting ITP per ASH case definitions are presented. Of these cases, 297 cases were serious and 103 were nonserious and reported a total of 461 EOI (347 serious, 114 nonserious).

Out of the 30 post-marketing, initial, primary dose cases, 11 reported TTO beyond 42 days from the day of vaccination and hence were considered outside the risk window and TTO was not reported in 5 cases. The mean and median TTO were 72.5 days and 35 days, respectively. The most frequently reported countries/territories of origin (n≥5) were the US (n=14), followed by Germany (n=5). These cases concerned 10 males in the age range from 28 to 83 years and 20 females in the age range from 22 to 97 years.

The frequency distribution of the MedDRA PTs of interest reported in post-marketing, primary dose cases is presented in Table 76 below. A single case may contain more than 1 EOI.

Table 76: Frequency of MedDRA PTs of Interest in Post-marketing, Primary Dose Cases Reporting Immune Thrombocytopenia With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Platelet count decreased	12	5	113	36
Thrombocytopenia	10	0	136	0
Immune thrombocytopenia	9	0	77	0
Thrombosis with thrombocytopenia syndrome	1	0	4	0

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

a: The MedDRA PTs of interest have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event of interest.

The EOI included platelet count decreased (n=17), thrombocytopenia (n=10), immune thrombocytopenia (n=9), and thrombosis with thrombocytopenia syndrome (n=1). Where reported (n=27), the outcomes were not resolved (n=13), resolved (n=7), resolving (n=4), fatal (n=2), and resolved with sequelae (n=1).

Fatal Post-marketing Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, there was 1 post-marketing, primary dose, fatal case with 2 fatal EOIs that met the ASH case definition for ITP with TTO beyond 42 days. This fatal case concerned a 73-year-old male with EOIs of thrombocytopenia and platelet count decreased, which was reported 271 days post-vaccination.

Booster Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 60 initial, booster dose cases reporting ITP were retrieved. Out of 60 cases, 8 (1 medically confirmed and 7 medically unconfirmed) initial cases reported as booster were identified to meet the ASH case definition for ITP. There were 7 serious cases and 1 nonserious and reported a total of 8 EOI (3 serious, 5 nonserious). Of these cases, 6 were heterologous and 2 were homologous.

All 8 booster cases received during the interval reporting period were reported from post-marketing sources (including spontaneous and solicited). None of the cases were reported from Janssen Sponsored Clinical Studies or Janssen Supported Clinical Studies.

Cumulatively, 15 (6 medically confirmed and 9 medically unconfirmed) cases reported as booster were identified to meet the ASH case definition for ITP. Of these cases, 12 were serious and 3 were nonserious and reported a total of 16 EOI (8 serious, 8 nonserious). Of these cases, 8 were heterologous and 7 were homologous. All 15 booster cases received cumulatively were reported from post-marketing sources (including spontaneous and solicited). None of the cases were reported from Janssen Sponsored Clinical Studies or Janssen Supported Clinical Studies.

Post-marketing Sources (Including Spontaneous and Solicited) Booster Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 8 post-marketing sources (including spontaneous and solicited), initial cases reported as booster were retrieved. These 8 post-marketing booster dose cases reported 8 EOI (3 serious; 5 nonserious).

Cumulatively, 15 (6 medically confirmed and 9 medically unconfirmed) post-marketing cases reported as booster were identified. Of these cases, 12 were serious and 3 were nonserious and reported a total of 16 EOI (8 serious; 8 nonserious).

Of these 8 post-marketing initial cases reported as booster, the most frequently reported countries/territories of origin (n≥2) were US (n=4) followed by Germany (n=2). These cases concerned 4 males in the age range from 55 to 75 years and 4 females in the age range from 33 to 81 years.

The frequency distribution of the MedDRA PTs of interest reported in post-marketing cases reported as booster is presented in Table 78 below.

Table 78: Frequency of MedDRA PTs of Interest in Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Immune Thrombocytopenia

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Platelet count decreased	2	5	3	8
HELLP syndrome	1	0	1	0

Key: HELLP=Haemolysis, Elevated liver enzymes, Low platelet count; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term

a: The MedDRA PTs of interest have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022).

The EOIs included platelet count decreased (n=7) and HELLP syndrome (n=1). The mean and median TTO were 61.6 days and 38 days, respectively. Where reported (n=5), the outcomes were not resolved (n=4) and resolved (n=1).

Fatal Post-marketing Booster Dose Cases

There were no fatal cases reported as booster which were retrieved from the search of the Company global safety database during the interval reporting period of 25 February 2022 to 24 August 2022.

Literature ICSR

No information was identified that would change the characterisation of risk.

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 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 is listed as AR in the SmPC, section 4.8. No new safety concern is detected here.

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 categorized 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.

Update on Missing Information

Use During Pregnancy

According to the cRMP (version 4.0; dated 09 December 2021), use during pregnancy is a missing information associated with the use of Ad26.COV2.S. This section will contain information on cases reporting use during pregnancy and use in breastfeeding women.

Results/Discussion
Primary Dose and Booster Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 479 (264 medically confirmed and 215 medically unconfirmed) primary dose and 91 (34 medically confirmed and 57 medically unconfirmed) booster dose cases were retrieved by the search strategy for use in pregnancy/use in breastfeeding women. Of these 570 interval cases, 37 did not meet the criteria for inclusion in this section (cases of congenital anomalies reported in patients and not related to pregnancy or lactation exposure). In 2 cases, placebo was given and Ad26.COV2.S was not involved. Additionally, 73 cases reported maternal exposure to vaccine >3 months before pregnancy and 15 reported paternal exposure to vaccine >2 weeks before pregnancy. Three cases concerned multiple patients without individual patient identifiers and 3 were duplicate cases. These 133 cases are not discussed further. Of the remaining 437 cases received during the interval reporting period, 66 were reported from Janssen Sponsored Clinical Studies, 8 from Janssen Supported Clinical Studies, and 363 from post-marketing sources (including spontaneous and solicited sources). During this period, 421 cases (167 serious; 254 nonserious) reporting exposure during pregnancy (including 2 linked cases reporting lactation exposure along with pregnancy exposure in the same baby and 1 reporting lactation exposure in an infant and pregnancy exposure in a foetus) and 16 (3 serious; 13 nonserious) reporting exposure only during lactation were identified. Cumulatively, 1,292 (572 medically confirmed and 720 medically unconfirmed) primary dose and 114 (36 medically confirmed and 78 medically unconfirmed) booster dose cases were retrieved by the search strategy for use in pregnancy/use in breastfeeding women. Of these 1,406 cases, 113 did not meet the criteria for inclusion in this section (cases of congenital anomalies reported in patients and not related to pregnancy or lactation exposure). In 10 cases, placebo was given and Ad26.COV2.S was not involved. Additionally, 118 cases reported maternal exposure to vaccine >3 months before pregnancy, 23 reported paternal exposure to vaccine >2 weeks before pregnancy, and 1 case reported vaccination after pregnancy. Nine cases concerned multiple patients without individual patient identifiers and 3were duplicate cases. These 277 cases are not discussed further. Of the remaining 1,129 cumulative cases received, 129 were reported from Janssen Sponsored Clinical Studies, 28 from Janssen Supported Clinical Studies, and 923 from post-marketing sources (including spontaneous and solicited sources). Cumulatively, 978 cases reporting exposure during pregnancy (including 4 reporting lactation exposure along with pregnancy exposure in the same baby and 2 reporting lactation exposure in an infant and pregnancy exposure in a foetus) and 151 reporting exposure only during lactation were identified.

Pregnancy Janssen Sponsored Clinical Studies Cases

During the reporting period of 25 February 2022 to 24 August 2022, 65 cases reporting use in pregnancy were retrieved from Janssen Sponsored Clinical Studies. Of the 65 cases, 27 were reported from VAC31518COV3001, 13 each from both VAC31518COV2004 and VAC31518COV3009, 6 from VAC31518COV3003, 5 from VAC31518COV2008, and 1 from VAC31518COV1001. Of these 65 cases, the most frequently reported countries/territories of origin were Brazil (n=19), followed by the US (n=17), and South Africa (n=13). These cases concerned 57 females, 6 males, and 2 did not report sex. The age range was from 19 to 43 years for maternal cases and 0 to 0.14 years for baby cases. Cumulatively, 128

(39 serious and 89 nonserious) cases from Janssen Sponsored Clinical Studies reporting exposure during pregnancy were identified (65 were reported from VAC31518COV3001, 34 from VAC31518COV3009, 15 from VAC31518COV2004, 8 from VAC31518COV3003, 5 from VAC31518COV2008 and 1 from VAC31518COV1001). These 128 cases comprised 106 maternal, 4 paternal exposure, and 18 linked to maternal cases (9 linked baby and 9 linked paternal). Where reported, maternal age ranged from 19 to 46 years with mean and median of 31.3 and 31.5 years, respectively. The 128 cumulative cases reported 110 unique pregnancies, of which 46 reported an outcome as follows: live birth without congenital anomaly (n=23), spontaneous abortion (n=14, including 1 case of missed abortion), elective abortion (n=4; 2 due to congenital anomalies: skeletal dysplasia and unspecified anomaly), ectopic pregnancy (n=2), intrauterine death, live birth with congenital anomaly (tracheomalacia), and still birth (n=1 case each). Of the 14 cases reporting the outcome of spontaneous abortion, there were 7 with exposure before conception/pregnancy, 4 with exposure during the first trimester of pregnancy, and for the remaining 3 timing of vaccine exposure was not reported.

Janssen Supported Clinical Studies Cases

During the reporting period of 25 February 2022 to 24 August 2022, 8 cases reporting use in pregnancy were retrieved from Janssen Supported Clinical Studies. Of the 8 cases, 5 were reported from VAC31518COV3012, 2 from VAC31518COV2012, and 1 from VAC31518COV3021. The reported countries/territories of origin were South Africa (n=6) and Thailand (n=2). All cases concerned adult females aged from 25 to 53 years. Cumulatively, 28 (27 serious and 1 nonserious) cases from Janssen Supported Clinical Studies reporting exposure during pregnancy were identified (24 from VAC31518COV3012 and 2 each from VAC31518COV2012 and VAC31518COV3021). All cases reported maternal exposure; where reported, maternal age ranged from 24 to 53 years with mean and median of 34.5 and 34.0 years, respectively. The 28 cumulative cases reported 28 unique pregnancies, of which 5 reported an outcome: live birth without congenital anomaly (n=3; in 1 case neonatal death in a "severely premature" baby was reported 4 days after delivery), and spontaneous abortion (n=2). Of the 2 cases reporting the outcome of spontaneous abortion, in 1 of them, the trimester of exposure was not reported and in the other the abortion occurred 21 days after the mother received the booster dose of Ad26.COV2.S at gestation of 13 weeks and 6 days.

Post-marketing Sources (Including Spontaneous and Solicited Sources) Cases

During the reporting period of 25 February 2022 to 24 August 2022, 348 (133 serious and 215 nonserious) post-marketing (including spontaneous and solicited sources) cases reporting exposure during pregnancy were retrieved. Of the 348 cases, 221 were from the following solicited sources: COVID-19 Vaccines International Pregnancy Exposure Registry (C-VIPER, n=219), and PPSOTH004154 and SafeVac 2.0 smartphone app (n=1 each). Of these 348 post-marketing cases, the most frequently reported countries/territories of origin were the Philippines (n=145), followed by South Africa (n=95), and the US (n=89). These 348 cases comprised 269 maternal, 38 baby, and 41 linked to maternal cases (27 linked baby, 13 booster, and 1 paternal). Where reported, maternal age ranged from 18 to 53 years with mean and median of 29.9 and 30.0 years, respectively. Cumulatively, 822 (279 serious and 543 nonserious) post-marketing cases reporting exposure during pregnancy were identified. Of the 822 cases, 535 were from the following solicited sources: C-VIPER (n=531), PPSOTH004154 (n=2), COVID-19 LIM (noncompany study) and SafeVac 2.0 (n=1 each). Of these 822 post-marketing cases, the most frequently reported countries/territories of origin were the US (n=437), followed by the Philippines (n=158), and South Africa (n=114). These 822 cases comprised 698 maternal, 2 baby, and 122 linked to maternal cases (104 linked baby, 16 linked booster, and 2 paternal). Where reported, maternal age ranged from 18 to 53 years with mean and median of 31.2 and 32.0 years, respectively.

The frequency distribution of additional AE in mother cases and baby AEs in baby cases reported in post-marketing cases during the interval reporting period and cumulatively are presented in Table 79 and Table 80 below, respectively. A single case may contain more than 1 event.

Table 79: Frequency Distribution of Additional Adverse Events in Mother Cases Reporting Exposure During Pregnancy With the Use of Ad26.COV2.S

MedDRA PTs	Number of Additional Adverse Events Reported During the Reporting Period[a]		Number of Additional Adverse Events Received Cumulatively[a]	
	Serious	Nonserious	Serious	Nonserious
Labour pain	37	19	42	19
Pain in extremity	3	43	5	138
Myalgia	4	37	8	101
Pyrexia	1	37	7	106
Chills	4	31	12	122
Headache	2	33	6	111
Fatigue	1	30	7	141
Malaise	1	25	8	93
Arthralgia	1	13	2	45
Vaccination site pain	8	5	8	5
COVID-19	1	9	2	21
Back pain	9	0	9	3
Injection site swelling	0	9	0	16
Nausea	0	9	3	37
Dyspnoea	2	3	6	5
Gestational hypertension	3	2	5	6

Key: COVID-19=Corona Virus Disease 2019; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term

a: The MedDRA PTs with a frequency ≥5 have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event.

Table 80: Frequency Distribution of Additional Adverse Events in Baby Cases Reporting Exposure During Pregnancy With the Use of Ad26.COV2.S

MedDRA PTs	Number of Additional Adverse Events Reported During the Reporting Period[a]		Number of Additional Adverse Events Received Cumulatively[a]	
	Serious	Nonserious	Serious	Nonserious
COVID-19	2	8	5	9
Large for dates baby	2	7	3	15
Ear infection	1	4	1	4
Gastrooesophageal reflux disease	2	3	5	4
Neonatal dyspnoea	5	0	10	0
Ankyloglossia congenital	4	0	4	0
Gastroenteritis	2	2	2	2
Premature baby	4	0	5	0
Blood glucose decreased	2	1	2	1
Breech presentation	3	0	4	0
Cough	0	3	0	3
Jaundice neonatal	2	1	4	3
Pyrexia	1	2	1	4
Weight gain poor	1	2	1	2
Acoustic stimulation tests abnormal	1	1	1	1
Death	2	0	2	0
Oral candidiasis	2	0	2	0
Rhinorrhoea	0	2	0	2
Small for dates baby	1	1	1	1
Suspected COVID-19	0	2	0	2

Key: COVID-19=Corona Virus Disease 2019; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term

a: The MedDRA PTs with a frequency ≥2 have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event.

The 348 interval cases reported 307 unique pregnancies of which 275 were prospective and 32 were retrospectively reported. The outcomes reported in these 307 pregnancies (including pregnancy ongoing or outcome not reported) are provided in Table 81.

Table 81: Unique Pregnancy Outcomes in Post-marketing Cases Reporting Exposure During Pregnancy With Ad26.COV2.S During the Reporting Period 25 February 2022 to 24 August 2022 (Cases=307)

Pregnancy Outcomes	Number of Pregnancy Outcomes
Live birth without congenital anomalies	69[a]
Ongoing pregnancy	17
Spontaneous abortion	16[a,b]
Live birth with congenital anomalies	9
Ectopic pregnancy	3
Blighted ovum	2
Intrauterine death	1
Maternal death	1
NR	191
Total	**309**

Key: AE=Adverse Event; NR=Not Reported

a: One case reported twins with different pregnancy outcomes; hence, 2 outcomes have been presented for 1 unique case in their respective outcome category.

b: One case reported twins; hence, 2 outcomes have been presented for 1 unique case.

Cumulatively, 822 cases reported 700 unique pregnancy cases, of which 614 were prospective and 86 were retrospectively reported. In 200 of the 700 unique pregnancy cases, an outcome was reported, as presented in Table 82. Of the 200 unique pregnancy cases, 15 reported the following congenital anomalies: ankyloglossia congenital (n=4), macrocephaly (n=2), buried penis syndrome, cardiac septal defect, cleft lip, congenital hydrocephalus, external auditory canal atresia, heart disease congenital, high foetal head, Kabuki make-up syndrome, labial tie, palatal disorder, pyelocaliectasis, pyloric stenosis, renal aplasia, spina bifida, ventricular septal defect (n=1 each). In addition to the 200 unique pregnancy cases presented in Table 82, and 2 reported unspecified congenital anomalies (foetal disorder and foetal malformation) and 2 reported other baby AE (foetal hypokinesia and ultrasound foetal abnormal) detected in an ongoing pregnancy or in a pregnancy with no reported outcome.

Table 82: Summary Table of Unique Pregnancy Outcomes Cumulatively through 24 August 2022; Cases=200 Unique Pregnancies

Pregnancy Outcome	Prospective Cases Number				Retrospective Cases Number				Total
	Timing of Exposure in Pregnancy				Timing of Exposure in Pregnancy				
	Before Conception	First Trimester	After First Trimester	Unknown	Before Conception	First Trimester	After First Trimester	Unknown	
Ectopic Pregnancy	0	0	0	0	3	0	0	2	5
Spontaneous Abortion[a]	0	6[a]	0	0	10[b]	19	0	21[c,d]	56
Stillbirth With Foetal Defects	0	0	0	0	0	0	1	0	1
Stillbirth Without Foetal Defects	0	0	0	0	0	1	0	0	1
Live Birth With Congenital Anomaly	0	5	7[e]	0	0	0	1	1	14
Live Birth Without Congenital Anomaly[a]	2	37[f,g]	59[h,i]	2	0	3[j]	9	11[k]	123
Intrauterine Death	0	0	0	0	0	0	1	0	1
Maternal Death	0	1	0	0	0	0	0	0	1
Blighted Ovum	0	0	0	0	0	0	0	2	2
Total[l]	2	49	66	2	13	23	12	37	204

Key: AE=Adverse Event; n=Number of Pregnancy Outcomes

a: One case [redacted] reported spontaneous abortion in a twin pregnancy at first trimester. Hence, the count for spontaneous abortion for this case is included as n=2.

b: One case [redacted] reported spontaneous abortion with AE in a twin pregnancy. Hence, the count for spontaneous abortion is included as n=2.

Rapporteur assessment comment:

Experience in pregnancy and breast-feeding women up to approximately end of 2021 was assessed within LEG38. Available data at that time was considered insufficient to justify changes of the product information.

During the interval 309 unique pregnancies were reported of which 9 reported congenital abnormalities and 16 spontaneous abortions. Those numbers are smaller than in the last PSUR reports ((25/381 cases) and (36/263 cases) and 10 to 15% estimated cases of miscarriages). No new safety concern is detected here.

Use in Breastfeeding Women

Janssen Sponsored Clinical Studies Cases

During the reporting period of 25 February 2022 to 24 August 2022, 1 case reporting use in a breastfeeding woman was retrieved from a Janssen Sponsored Clinical Study. This nonserious case reported 1 nonserious event from VAC31518COV3001. The country/territory of origin was [redacted] Age and sex were unspecified in this case. The event included exposure via breast milk (n=1) with unknown outcome.

Janssen Supported Clinical Studies Cases

During the reporting period no cases reporting use in breastfeeding women were retrieved from Janssen Supported Clinical Studies.

Post-marketing Sources (Including Spontaneous and Solicited Sources) Cases

The administration of Ad26.COV2.S to breastfeeding women was reported in 15 (3 medically confirmed and 12 medically unconfirmed) cases in the reporting period. Of these 15 cases, none came from solicited sources, and 3 were serious and 12 were nonserious. All 15 were unique lactation cases: 9 were nonserious baby (3 had baby AEs and are presented in Table 83) and 6 were maternal without associated baby AEs. Of the 6 maternal cases, 3 were serious reporting the following serious AEs in addition to maternal exposure during breastfeeding: arthralgia, dizziness, headache, injection site pain, myalgia, pyrexia, and tachycardia.

A frequency distribution of AEs experienced by babies in the interval reporting period and cumulatively are presented below in Table 83.

Table 83: Frequency Distribution of Baby Adverse Events in Cases Reporting Exposure During Breastfeeding With Ad26.COV2.S During the Reporting Period 25 February 2022 to 24 August 2022

MedDRA PTs	Number of Additional Adverse Events Reported During the Reporting Period[a]		Number of Additional Adverse Events Received Cumulatively[a]	
	Serious	Nonserious	Serious	Nonserious
Adverse event	0	1	0	1
Apathy	0	1	0	2
Asthenia	0	1	0	1
Decreased appetite	0	1	0	2
Diarrhoea	0	1	0	2
Fatigue	0	1	0	1
Illness	0	1	0	1
Pyrexia	0	1	0	12
Somnolence	0	1	0	3
Vomiting	0	1	0	3

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: The additional adverse events were sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022).

Cumulatively, administration of Ad26.COV2.S to a lactating mother followed by breastfeeding of a baby was reported in 150 (53 medically confirmed and 97 medically unconfirmed) cases. Of these 150 cases, 3 came from solicited sources (2 from social media and 1 from COVID-19 LIM), and 12 were serious and 138 nonserious. The 12 serious cases were comprised of 7 maternal, 3 baby and 2 linked mother cases. These 150 cases reported 135 unique lactation cases. These 150 cases were comprised of 118 baby, 17 maternal, and 15 linked mother cases. Of the 118 baby cases, baby AEs were reported in 26 (2 of which were serious). These 26 cases reported 60 additional events (3 serious, 57 nonserious) with pyrexia as the most frequently reported (n=12).

A review of these cases, including demographics, concomitant medications, concurrent conditions/medical history, outcome, and seriousness, is consistent with what is currently known about the missing information of use during pregnancy and use in breastfeeding women.

Booster Dose

Cumulatively, 100 (28 medically confirmed and 72 medically unconfirmed) cases reported as booster were identified. Of these cases, 39 were heterologous and 61 were homologous. These cases are discussed in the above section along with the primary dose cases. Of the 100 cumulative cases reported as booster, 18 were reported from Janssen Sponsored Clinical Studies (VAC31518COV3001 [n=15], VAC31518COV3009 [n=2] and VAC31518COV3003 [n=1]), 1 from a Janssen Supported Clinical Study (VAC31518COV3021), and 81 from post-marketing sources (including spontaneous and solicited sources).

Literature ICSR

One ICSR literature case was received and reviewed during the reporting period of 25 February 2022 to 24 August 2022. The case concerned a 30-year-old female (gravida 1, para 0) who received Ad26.COV2.S in the second trimester of pregnancy. The patient's past medical history was notable only for heterozygous factor V Leiden deficiency (not currently on treatment) and the patient had no obstetric issues. The patient experienced an all-over body rash 1 week after vaccination. Approximately 2 weeks later, the patient presented with neurological symptoms of left facial weakness, with significant bifacial paresis and bilateral hand paraesthesia. The facial diplegia variant of GBS was diagnosed; lumbar puncture demonstrated elevated cerebrospinal fluid protein and nerve conduction study found evidence of a diffuse sensorimotor demyelinating polyneuropathy. The patient fully recovered to baseline 4 weeks after presentation and at 40 weeks and 5 days gestation, gave birth to a healthy baby via normal

spontaneous vaginal delivery without complications. No new information was identified for the missing information of use during pregnancy.

MAH Discussion

No new critical safety information was identified during the reporting period for the missing information of use during pregnancy and use in breastfeeding women. In addition, a COVID-19 Vaccines International Pregnancy Exposure Registry (C-VIPER) an annual report covering the period 01 June 2021 to 31 May 2022 concluded that no safety concerns were identified for either mother or child in cases reporting pregnancy.

MAH Conclusion

Based on the evaluation of the cases, and review of safety from other sources, the information is consistent with the information known about use during pregnancy and lactation. The Company will continue to closely monitor the use of Ad26.COV2.S during pregnancy and lactation.

Use in Breastfeeding Women

Information on use in breastfeeding women is covered in the section above, Section Use During Pregnancy.

Rapporteur assessment comment:

The number of breastfeeding cases is with 150 cases cumulatively and 15 in the interval (primary series) and 100 cases of booster dosing still very limited and continuous monitoring as missing information is supported.

Use in Immunocompromised Patients

According to the cRMP (version 4.0; dated 09 December 2021), use in immunocompromised patients is considered missing information for Ad26.COV2.S.

Primary Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 1,005 (582 medically confirmed and 423 medically unconfirmed) initial, primary dose cases reporting use in immunocompromised patients were identified. Of these 1,005 cases, 714 were serious and 291 were nonserious and reported a total of 4,239 events (2,441 serious; 1,798 nonserious).

Of these 1,005 primary dose cases received during the interval reporting period, 275 were reported from Janssen Sponsored Clinical Studies, 95 from Janssen Supported Clinical Studies, and 635 from post-marketing sources (including spontaneous and solicited).

Cumulatively, 8,043 (3,435 medically confirmed and 4,608 medically unconfirmed) primary dose cases reporting use in immunocompromised patients were identified. Of these cases, 4,299 were serious and 3,744 were nonserious and reported a total of 45,033 events (18,200 serious; 26,833 nonserious). Of the 8,043 cumulative primary dose cases received, 838 were reported from Janssen Sponsored Clinical Studies, 407 from Janssen Supported Clinical Studies, and 6,798 from post-marketing sources (including spontaneous and solicited cases).

Janssen Sponsored Clinical Studies Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 275 initial, primary dose cases reporting use in immunocompromised patients were retrieved from Janssen Sponsored Clinical Studies. Of the 275 cases, 179 were from VAC31518COV3001, 82 from VAC31518COV3009, 9 from

VAC31518COV2008, 3 from VAC31518COV1001, and 2 from VAC31518COV3005. These 275 cases reported 328 events (291 serious; 37 nonserious). Of these 275 cases, the most frequently reported countries/territories of origin (n≥29) were the US (n=151), followed by South Africa (n=31) and Brazil (n=29). These cases concerned 156 males and 119 females. The age range was from 19 to 87 years. The most frequently reported events in these retrieved cases (≥5) included thrombocytopenia (n=25), pneumonia (n=10), deep vein thrombosis (n=6), and asthma and osteoarthritis (n=5 each). The mean and median TTO were 355.5 and 359 days, respectively. Where reported (n=317), the outcomes were resolved (n=168), not resolved (n=62), resolving (n=50), fatal (n=27), and resolved with sequelae (n=10). Of note, platelet counts in clinical trials were being monitored as a protocol mandated procedure. Most of the reported events of thrombocytopenia were nonserious (22 out of 25) with latencies ranging between 244 and 507 days post initial dose.

Janssen Supported Clinical Studies Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 95 initial, primary dose cases reporting use in immunocompromised patients were retrieved from Janssen Supported Clinical Studies. Of the 95 cases, 50 were from VAC31518COV3012, 36 from VAC31518COV3021, and 9 from VAC31518COV2012. These 95 cases reported 98 events (95 serious; 3 nonserious). Of these 95 cases, the reported countries/territories of origin were South Africa (n=86), followed by Thailand (n=9). These cases concerned 79 females and 16 males. The age range was from 23 to 79 years.

The most frequently reported events in these retrieved cases (≥2) included COVID-19 (n=92) and gastroenteritis (n=2). The mean and median TTO were 309.8 and 349.5 days, respectively. Where reported (n=97), the outcomes were resolved (n=83), fatal (n=11), and resolving (n=3).

Post-marketing Sources (Including Spontaneous and Solicited) Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 635 post-marketing sources (including spontaneous and solicited), initial, primary dose cases reporting use in immunocompromised patients were retrieved. These 635 initial, post-marketing, primary dose cases reported 3,813 events (2,055 serious; 1,758 nonserious). Cumulatively, 6,798 (2,190 medically confirmed and 4,608 medically unconfirmed) post-marketing, primary dose cases reporting use in immunocompromised patients were identified. Of these cases, 3,190 were serious and 3,608 were nonserious and reported a total of 43,559 events (16,905 serious; 26,654 nonserious). Of these 635 post-marketing, initial, primary dose cases, the most frequently reported countries/territories of origin (n≥29) were the US (n=325), followed by Spain (n=36), and Canada (n=29). These cases concerned 401 females, 202 males, and 32 did not report sex. The age range was from 14 to 90 years. The frequency distribution of relevant medical history PTs reported in the 635 cases is presented in Table 85 below. A single case may contain more than 1 relevant medical history.

Table 85: Frequency Distribution of Relevant Medical History PTs Involving the Use of Ad26.COV2.S and Reporting Use in Immunocompromised Patients

Medical History	Count of Medical History PTs During the Reporting Period[a]	Count of Medical History PTs Cumulatively
Drug hypersensitivity	239	2,962
Asthma	80	942
Seasonal allergy	74	1,207
Food allergy	46	1,189
Rheumatoid arthritis	45	251
Hypersensitivity	44	505
Crohn's disease	34	141
Psoriasis	30	193
Autoimmune thyroiditis	25	206
Allergy to animal	22	301
Psoriatic arthropathy	18	89
Colitis ulcerative	16	83
Anaphylactic reaction	13	74
Mite allergy	13	233
Multiple sclerosis	12	108
Allergy to arthropod sting	11	126
Multiple allergies	10	121

Key: PT=Preferred Term

a: The medical history PTs of interest with frequency ≥10 have been presented by decreasing order for the reporting period (25 February 2022 to 24 August 2022).

b: A single case may report more than 1 relevant medical history.

The frequency distribution of the MedDRA PTs reported in post-marketing, primary dose cases is presented in Table 86 below. A single case may contain more than 1 event.

Table 86: Frequency of MedDRA PTs in Post-marketing, Primary Dose Cases Reporting Use in Immunocompromised Patients With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Headache	27	79	290	1,668
Pyrexia	21	68	236	1,202
Fatigue	24	56	209	1,361
COVID-19	28	34	126	114
Vaccination failure	60	0	271	0
Pain	13	41	118	789
Suspected COVID-19	4	47	18	109
Pain in extremity	16	34	174	737

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term; SARS-CoV-2=Severe Acute Respiratory Syndrome Coronavirus-2

a: The MedDRA PTs with a frequency ≥50 have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event.

The most frequently reported events in these retrieved cases (n≥50) included headache (n=106), pyrexia (n=89), fatigue (n=80), COVID-19 (n=62), vaccination failure (n=60), pain (n=54), suspected COVID-19 (n=51), and pain in extremity (n=50). The mean and median TTO were 84.0 and 12 days, respectively. Where reported (n=2,923), the outcomes were not resolved (n=1,501), resolved (n=781), fatal (n=353), resolving (n=263), and resolved with sequelae (n=25).

As presented in Table 87 below, the majority of the MedDRA PTs referring to vaccination failure occurred in cases which did not meet the case definition of lack of efficacy (presented in Section 15.5, Vaccination Failure, Lack of Efficacy/Effectiveness).

Table 87: Distribution of MedDRA PTs by Case Definition Criteria of Vaccination Failure

Case Definition Criteria	Number of PTs		
	COVID-19	Vaccination failure	Suspected COVID-19
Confirmed vaccination failure (medically confirmed, TTO>14 days and positive COVID-19 testing)	4 serious 0 nonserious	0	0
Suspected vaccination failure (medically confirmed, TTO>14 days and COVID-19 testing not reported)	0	0	0
Case definition not met	24 serious 34 nonserious	60 serious 0 nonserious	4 serious 47 nonserious

Key: COVID-19=Coronavirus Disease-2019; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term; TTO=Time to Onset

Fatal Post-marketing Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 24 post-marketing, initial, primary dose fatal cases with 353 fatal events were retrieved. The most frequently reported fatal events (n≥5) were death (n=12), COVID-19 (n=8), acute respiratory failure and COVID-19 pneumonia (n=7 each), SARS-CoV-2 test positive (n=6); and condition aggravated, dyspnoea, and pneumonia (n=5 each). Most of the fatal events occurred in the context of COVID-19 infection.

Booster Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 375 (103 medically confirmed and 272 medically unconfirmed) initial cases reported as booster were identified. There were 221 serious and 154 nonserious cases and reported a total of 1,308 events (430 serious; 878 nonserious). Of these cases, 220 were heterologous and 155 were homologous. Of these 375 cases reported as booster during the interval, 19 were reported from Janssen Sponsored Clinical Studies, 12 from Janssen Supported Clinical Studies, and 344 from post-marketing sources (including spontaneous and solicited). Cumulatively, 595 (179 medically confirmed and 416 medically unconfirmed) cases reported as booster were identified. Of these cases, 320 were serious and 275 were nonserious and reported a total of 2,435 events (776 serious; 1,659 nonserious). Of these cases, 318 were homologous and 277 were heterologous. Of the 595 cumulative booster dose cases received, 40 were reported from Janssen Sponsored

Clinical Studies, 14 from Janssen Supported Clinical Studies, and 541 from post-marketing sources (including spontaneous and solicited cases).

Janssen Sponsored Clinical Studies Booster Dose Cases

During the interval reporting period of 25 February 2022 to 24 August 2022, 19 initial cases reported as booster were retrieved from Janssen Sponsored Clinical Studies. Of the 19 cases, 18 were from VAC31518COV3001 and 1 from VAC31518COV3005. These 19 cases reported 27 events (20 serious; 7 nonserious). Of these 19 cases, the most frequently reported countries/territories of origin (n≥3) were the US (n=9), followed by South Africa (n=4) and Brazil (n=3). These cases concerned 12 females and 7 males. The age range was from 32 to 76 years.

The most frequently reported events in these retrieved cases (n≥2) included thrombocytopenia (n=7), and chronic obstructive pulmonary disease and diverticulitis (n=2 each). The mean and median TTO were 149.4 days and 142.0 days, respectively. The reported outcomes were resolved (n=18), resolving (n=6), not resolved (n=2), and resolved with sequelae (n=1). Of note, platelet counts in clinical trials were being monitored as a protocol mandated procedure. All the reported events of thrombocytopenia were nonserious with latencies ranging between 0 to 76 days post-vaccination.

Janssen Supported Clinical Studies Booster Dose Cases

During the interval reporting period of 25 February 2022 to 24 August 2022, 12 initial cases reported as booster were retrieved from Janssen Supported Clinical Studies. Of the 12 cases, 11 were from VAC31518COV3021 and 1 from VAC31518COV2012. These 12 cases reported 12 events (11 serious; 1 nonserious). For these 12 cases, the reported countries/territories of origin were South Africa (n=11) and Thailand (n=1). These cases concerned 11 females and 1 male. The age range was from 25.5 to 83 years. The reported event was COVID-19 in all retrieved cases. The mean and median TTO were 167.1 days and 162.0 days, respectively. The reported outcomes were resolved (n=10) and fatal (n=2).

Post-marketing Sources (Including Spontaneous and Solicited) Booster Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 344 post-marketing sources (including spontaneous and solicited), initial cases reported as booster were retrieved. These 344 post-marketing, initial, booster dose cases reported 1,269 events (399 serious; 870 nonserious). Cumulatively, 541 (125 medically confirmed and 416 medically unconfirmed) post-marketing, cases reported as boosters were identified. Of these cases, 291 cases were serious and 250 were nonserious and reported a total of 2,364 events (735 serious; 1,629 nonserious). Of these 344 post-marketing, initial cases reported as booster, the most frequently reported countries/territories of origin (n≥21) were the US (n=236), followed by Brazil (n=58) and Canada (n=21). These cases concerned 212 females and 112 males. The age range was from 13 to 85 years. The frequency distribution of relevant medical history PTs reported in the 344 cases is presented in Table 89 below. A single case may contain more than 1 relevant medical history.

Table 89: Frequency Distribution of Relevant Medical History PTs in Post-marketing Cases Reported as Booster Dose Involving the Use of Ad26.COV2.S and Reporting Use in Immunocompromised Patients

Medical History	Count of Medical History PTs During the Reporting Period[a]	Count of Medical History PTs Cumulatively
Drug hypersensitivity	168	294
Asthma	45	66
Food allergy	44	74
Hypersensitivity	41	60
Rheumatoid arthritis	39	51
Crohn's disease	25	35
Seasonal allergy	21	46
Ankylosing spondylitis	15	17
Psoriasis	11	20
Psoriatic arthropathy	11	15
Colitis ulcerative	10	20
Autoimmune thyroiditis	7	11
Immunodeficiency	6	11
Rubber sensitivity	6	12
Allergy to arthropod sting	5	9
Iodine allergy	5	7
Multiple allergies	5	15
Multiple sclerosis	5	6
Rhinitis allergic	5	7

Key: PT=Preferred Term

a: The medical history PTs of interest with frequency ≥5 have been presented by decreasing order for the reporting period (25 February 2022 to 24 August 2022).

b: A single case may report more than 1 relevant medical history.

The frequency distribution of the MedDRA PTs reported in post-marketing cases reported as booster is presented in Table 90 below. A single case may contain more than 1 event.

Table 90: Frequency of MedDRA PTs in Post-marketing Cases Reported as Booster Dose With the Use of Ad26.COV2.S and Reporting Use in Immunocompromised Patients

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Vaccination failure	113	0	136	0
COVID-19	10	102	15	113
Off label use	0	93	0	126
Suspected COVID-19	3	57	3	73
Inappropriate schedule of product administration	0	50	0	79
Pyrexia	3	20	9	44
Pain in extremity	4	16	10	41
Headache	1	18	8	41
Pain	3	16	6	35
Arthralgia	2	16	4	22
Fatigue	3	13	5	38
Dysgeusia	0	15	0	18
Chills	0	12	1	30
Diarrhoea	1	10	1	18
Feeling abnormal	0	10	2	24
Nausea	1	9	8	23

Key: COVID-19=Coronavirus Disease 2019; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term

a: The MedDRA PTs with a frequency ≥10 have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event.

The most frequently reported events in these retrieved cases (n≥50) included vaccination failure (n=113), COVID-19 infection (n=112), off label use (n=93), suspected COVID-19 infection (n=60), and inappropriate schedule of product administration (n=50). The mean and median TTO were 142.3 days and 64 days, respectively. Where reported (n=694), the outcomes were not resolved (n=309), resolved (n=233), resolving (n=131), fatal (n=17), and resolved with sequelae (n=4).

As presented in Table 91 below, the majority of MedDRA PTs referring to vaccination failure were reported in cases which did not meet the case definition for lack of efficacy (See Section 15.5, Vaccination Failure, Lack of efficacy/Effectiveness).

Table 91: Distribution of MedDRA PTs by Case Definition Criteria of Vaccination Failure

Case Definition Criteria	Number of PTs		
	Vaccination failure	COVID-19	Suspected COVID-19
Confirmed vaccination failure (medically confirmed, TTO>14 days and positive COVID-19 testing)	10 serious 0 nonserious	4 serious 0 nonserious	0 serious 2 nonserious
Suspected vaccination failure (medically confirmed, TTO>14 days and COVID-19 testing not reported)	0	0	0
Case definition not met	103 serious 0 nonserious	6 serious 102 nonserious	3 serious 55 nonserious

Key: COVID-19=Coronavirus Disease-2019; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term; TTO=Time to Onset

Fatal Post-marketing Booster Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 6 initial, fatal cases reported as booster with 17 fatal events were retrieved. The reported fatal events were acute respiratory distress syndrome and cough (n=2 each), and asthenia, COVID-19 infection, COVID-19 pneumonia, decreased appetite, diarrhoea, dysarthria, dyspnoea, gait inability, GBS, oxygen saturation decreased, paraesthesia, pyrexia, and vision blurred (n=1 each).

Literature ICSR

No new information was identified on the use of Ad26.COV2.S in immunocompromised patients.

MAH Discussion

Based on the evaluation of the cases, and review of safety from other sources, the nature of reported AEs in immunocompromised patients is consistent with the known safety profile of Ad26.COV2.S and with

what is expected in this patient population. The warnings and precaution section of the CCDS states that immunocompromised persons including individuals receiving immunosuppressant therapy, may have a diminished immune response to Ad26.COV2.S.

MAH Conclusion

The Company will continue to closely monitor use in immunocompromised patients as missing information.

Rapporteur assessment comment:

During the reporting period of 25 February 2022 to 24 August 2022, 635 post-marketing sources (including spontaneous and solicited), initial, primary dose cases reporting use in immunocompromised patients were retrieved, reporting 3,813 events. Cumulatively, 6,798 (2,190 medically confirmed and 4,608 medically unconfirmed) post-marketing, primary dose cases reporting use in immunocompromised patients were identified.

The most frequently reported events in the cases retrieved in the interval (n≥50) included headache (n=106), pyrexia (n=89), fatigue (n=80), COVID-19 (n=62), vaccination failure (n=60), pain (n=54), suspected COVID-19 (n=51), and pain in extremity (n=50).

No new safety concern is identified here with primary vaccination or booster dosing.

Use in Patients with Autoimmune or Inflammatory Disorders

Use in patients with autoimmune or inflammatory disorders is considered missing information for Ad26.COV2.S according to the cRMP (version 4.0; dated 09 December 2021).

Primary Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 685 (437 medically confirmed and 248 medically unconfirmed) initial, primary dose cases reporting use in patients with autoimmune or inflammatory disorders were identified. Of these 685 cases, 490 were serious and 195 were nonserious and reported a total of 2,712 events (1,653 serious; 1,059 nonserious). Of these 685 primary dose cases received during the interval reporting period, 226 were reported from Janssen Sponsored Clinical Studies, 71 from Janssen Supported Clinical Studies, and 388 from post-marketing sources (including spontaneous and solicited).

Cumulatively, 4,658 (2,490 medically confirmed and 2,168 medically unconfirmed) primary dose cases reporting use in patients with autoimmune or inflammatory disorders were identified. Of these cases 2,938 were serious and 1,720 were nonserious and reported a total of 23,678 events (11,974 serious; 11,704 nonserious). Of the 4,658 cumulative primary dose cases received, 702 were reported from Janssen Sponsored Clinical Studies, 489 from Janssen Supported Clinical Studies, and 3,467 from post-marketing sources (including spontaneous and solicited cases).

Janssen Sponsored Clinical Studies Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 226 initial, primary dose cases reporting use in patients with autoimmune or inflammatory disorders were retrieved from Janssen Sponsored Clinical Studies. Of the 226 cases, 142 were from VAC31518COV3001, 70 from VAC31518COV3009, 10 from VAC31518COV2008, 2 from VAC31518COV1001, and 1 each from VAC31518COV3005 and VAC31518COV3003. These 226 cases

reported 273 events (235 serious; 38 nonserious). Of these 226 cases, the most frequently reported countries/territories of origin (n≥20) were the US (n=111), followed by Brazil (n=33) and South Africa (n=20). These cases concerned 136 females and 90 males. The age range was from 24 to 93 years.

The most frequently reported events (≥5) included thrombocytopenia (n=26), osteoarthritis (n=10), cellulitis and deep vein thrombosis (n=6 each), and diverticulitis (n=5). The mean and median TTO were 357.0 and 367.0 days, respectively. Where reported (n=269), the outcomes were resolved (n=151), resolving (n=44), not resolved (n=29), fatal (n=27), and resolved with sequelae (n=18). Of note, monitoring of platelet levels was a protocol mandated procedure in Company-sponsored clinical trials as part of the TTS AESI which artificially incremented the number of thrombocytopenia cases in CTs. Twenty-four of the 26 reported events of thrombocytopenia were nonserious with a latency ranging between 57 and 498 days post-primary dose, none were considered related by the investigator.

Janssen Supported Clinical Studies Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 71 initial, primary dose cases reporting use in patients with autoimmune or inflammatory disorders were retrieved from Janssen Supported Clinical Studies. Of the 71 cases, 38 were from VAC31518COV3021, 31 from VAC31518COV3012, and 2 from VAC31518COV2012. These 71 cases reported 72 events (70 serious; 2 nonserious). The countries/territories of origin in these 71 cases were from South Africa (n=69) and Thailand (n=2). These cases concerned 53 females and 18 males. The age range was from 29 to 89 years.

The events reported in these 71 cases included COVID-19 (n=70), followed by gastroenteritis and maternal exposure before pregnancy (n=1 each). Latencies ranged from 23 to 473 days post-primary dose with mean and median TTO of 326.9 and 354.5 days, respectively. Where reported (n=71), the outcomes were resolved (n=66) and fatal (n=5).

Post-marketing Sources (Including Spontaneous and Solicited) Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 388 post-marketing sources (including spontaneous and solicited), initial, primary dose cases reporting use in patients with autoimmune or inflammatory disorders were retrieved. These 388 post-marketing, initial, primary dose cases reported 2,367 events (1,348 serious; 1,019 nonserious). Cumulatively, 3,467 (1,299 medically confirmed and 2,168 medically unconfirmed) post-marketing, primary dose cases reporting use in patients with autoimmune or inflammatory disorders were identified. Of these cases, 1,880 were serious and 1,587 were nonserious and reported a total of 22,289 events (10,759 serious; 11,530 nonserious).

Of these 388 post-marketing, initial, primary dose cases, the most frequently reported countries/territories of origin (n≥27) were the US (n=188), followed by Spain (n=42) and Canada (n=27). These cases concerned 235 females, 126 males, and 27 did not report sex. The age range was from 14 to 90 years.

The frequency distribution of the MedDRA PTs reported in post-marketing, primary dose cases is presented in Table 93 below. A single case may contain more than 1 event.

Table 93: Frequency of MedDRA PTs reported in Post-marketing, Primary Dose Cases Reporting Use in Patients With Autoimmune or Inflammatory Disorders With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Headache	11	50	143	634
Pyrexia	13	48	130	468
Fatigue	14	37	106	562
COVID-19	21	18	110	58
Pain	10	28	69	380
Suspected COVID-19	4	27	17	51
Vaccination failure	31	0	162	0
Malaise	16	14	61	184
Myalgia	4	26	48	239
Nausea	5	24	67	261
Pain in extremity	7	22	86	357
Chills	5	21	54	335
Dyspnoea	16	9	152	121
Arthralgia	6	18	55	271
Dizziness	6	16	81	226
Condition aggravated	12	7	86	80
SARS-CoV-2 test positive	15	3	73	10
Asthenia	6	11	78	165
Thrombosis	17	0	172	0
Chest pain	12	4	92	65
Cough	8	7	50	67
Diarrhoea	3	11	28	132
Feeling abnormal	4	10	25	157
Death	13	0	82	0
Vomiting	9	4	59	102
Back pain	3	9	33	72
Decreased appetite	3	9	20	71
Laboratory test	10	2	46	16
Vaccination site pain	0	12	4	43
Anticoagulant therapy	11	0	82	1
Gait disturbance	6	5	44	61
Injection site pain	0	11	11	212
Paraesthesia	3	8	46	120
Muscle spasms	2	8	14	62
Rash	2	8	21	83

Key: COVID-19=Coronavirus disease-2019; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term; SARS-CoV-2=Severe Acute Respiratory Syndrome Coronavirus-2

a: The MedDRA PTs with a frequency ≥10 have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event.

The most frequently reported events (n≥30) included headache and pyrexia (n=61 each), fatigue (n=51), COVID-19 (n=39), pain (n=38), suspected COVID-19 and vaccination failure (n=31 each), and malaise and myalgia (n=30 each). The mean and median TTO were 106.0 and 29.5 days, respectively. Where reported (n=1,707), the outcomes were not resolved (n=736), resolved (n=515), fatal (n=290), resolving (n=160), and resolved with sequelae (n=6).

The frequency distribution of relevant medical history PTs reported in the 388 cases is presented in Table 94 below. A single case may contain more than 1 relevant medical history PT.

Table 94: Frequency Distribution of Relevant Medical History PTs Involving the Use of Ad26.COV2.S and Reporting Use in Patients With Autoimmune or Inflammatory Disorders

Medical History	Count of Medical History PTs During the Reporting Period[a]	Count of Medical History PTs Cumulatively
Diabetes mellitus	53	700
Hypothyroidism	50	539
Rheumatoid arthritis	45	251
Crohn's disease	34	141
Psoriasis	30	193
Autoimmune thyroiditis	25	206
Arthritis	19	245
Psoriatic arthropathy	18	89
Colitis ulcerative	16	83
Multiple sclerosis	12	108
Ankylosing spondylitis	8	38
Systemic lupus erythematosus	7	98
Autoimmune hypothyroidism	6	11
Basedow's disease	6	46
Coeliac disease	6	66
Thyroid disorder	6	159
Autoimmune disorder	5	94
Sjogren's syndrome	5	46
Type 1 diabetes mellitus	5	85
Hyperthyroidism	4	45
Immune thrombocytopenia	4	29

Key: PT=Preferred Term

a: The medical history PTs of interest with frequency ≥4 have been presented by decreasing order for the reporting period (25 February 2022 to 24 August 2022).

b: A single case may report more than 1 relevant medical history.

Fatal Post-marketing Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 24 post-marketing, initial, primary dose fatal cases with 290 fatal events were retrieved. The most frequently reported fatal events (n≥5) were death (n=13, mostly in polymorbid patients in context of COVID-19 infection) and COVID-19 infection (n=5).

Booster Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 205 (71 medically confirmed and 134 medically unconfirmed) initial cases reported as booster were identified. There were 95 serious and 110 nonserious cases and reported a total of 661 events (222 serious; 439 nonserious). Of these cases, 103 were heterologous and 102 were homologous. Of these 205 cases reported as booster during the interval, 15 were reported from Janssen Sponsored Clinical Studies, 7 from Janssen Supported Clinical Studies, and 183 from post-marketing sources (including spontaneous and solicited). Cumulatively, 351 (130 medically confirmed and 221 medically unconfirmed) cases reported as booster were identified. Of these cases, 148 were serious and 203 were nonserious and reported a total of 1,373 events (407 serious; 966 nonserious). Of these cases, 217 were homologous and 134 were heterologous.

Of the 351 cumulative booster dose cases received, 34 were reported from Janssen Sponsored Clinical Studies, 9 from Janssen Supported Clinical Studies, and 308 from post-marketing sources (including spontaneous and solicited cases).

Janssen Sponsored Clinical Studies Booster Dose Cases

During the interval reporting period of 25 February 2022 to 24 August 2022, 15 initial cases reported as booster were retrieved from Janssen Sponsored Clinical Studies. All cases were from VAC31518COV3001. These 15 cases reported 21 events (14 serious; 7 nonserious). The countries/territories of origin in these 15 cases were from the US (n=9), followed by Brazil (n=3), and Argentina, Colombia and Mexico (n=1 each). These cases concerned 9 females and 6 males. The age range was from 35 to 76 years.

The most frequently reported events (n≥2) included thrombocytopenia (n=5) and diverticulitis (n=2). The mean and median TTO were 167.3 and 142.0 days, respectively. Where reported (n=19), the outcomes were resolved (n=10), resolving (n=6), not resolved (n=2), and resolved with sequelae (n=1).

Janssen Supported Clinical Studies Booster Dose Cases

During the interval reporting period of 25 February 2022 to 24 August 2022, 7 initial cases reported as booster were retrieved from a Janssen Supported Clinical Study. All cases were from VAC31518COV3021. These 7 cases reported 7 serious events. The reported country/territory of origin for all 7 cases was South Africa. These cases concerned 5 females and 2 males. The age range was from 44 to 83 years. All cases reported the event COVID-19. The mean and median TTO were 199.1 and 186.0 days, respectively. The outcomes reported were resolved (n=4) and fatal (n=3).

Post-marketing Sources (Including Spontaneous and Solicited) Booster Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 183 post-marketing sources (including spontaneous and solicited), initial cases reported as booster were retrieved. These 183 post-marketing, booster dose cases reported 633 events (201 serious; 432 nonserious). Cumulatively, 308 (87 medically confirmed and 221 medically unconfirmed) post-marketing, cases reported as booster were identified. Of these cases, 130 were serious and 178 were nonserious and reported a total of 1,324 events (383 serious; 941 nonserious). Of these 183 post-marketing, initial cases reported as booster, the most frequently reported countries/territories of origin (n≥19) were the US (n=100), followed by Brazil (n=44) and Canada (n=19). These cases concerned 114 females, 62 males, and 7 did not report sex. The age range was from 20 to 88 years. The frequency distribution of the MedDRA PTs reported in post-marketing cases reported as booster is presented in Table 96 below. A single case may contain more than 1 event.

The most frequently reported events (n>20) included off label use (n=70), COVID-19 (n=50), vaccination failure (n=31), inappropriate schedule of product administration (n=29), and suspected COVID-19 (n=23). The mean and median TTO were 140.8 and 73.0 days, respectively. Where reported (n=336), the outcomes were not resolved (n=130), resolved (n=124), resolving (n=69), and fatal (n=13).

Table 96: Frequency of MedDRA PTs reported in Post-marketing Cases Reported as Booster Dose With the Use of Ad26.COV2.S and Reporting Use in Patients With Autoimmune or Inflammatory Disorders

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Off label use	0	70	0	107
COVID-19	6	44	9	49
Vaccination failure	31	0	37	0
Inappropriate schedule of product administration	0	29	0	62
Suspected COVID-19	1	22	1	27
Pain	2	11	5	24
Pyrexia	2	10	5	25
Arthralgia	1	10	2	17
Fatigue	5	6	6	26
Pain in extremity	1	10	5	22
Headache	1	6	3	22
Chills	1	5	1	17
Dyspnoea	3	3	4	5
Influenza	0	6	0	9
Malaise	1	5	3	11
Anticoagulant therapy	5	0	7	0
Chest pain	3	2	7	8
Dysgeusia	0	5	0	6
Injection site pain	0	5	0	10
Nausea	1	4	7	8
Peripheral swelling	0	5	3	5
SARS-CoV-2 test positive	2	3	4	5

Key: COVID-19=Coronavirus disease 2019; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term; SARS-CoV-2=Severe Acute Respiratory Syndrome Coronavirus-2

a: The MedDRA PTs with a frequency ≥5 have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event.

The frequency distribution of relevant medical history PTs reported in the 183 initial cases is presented in Table 97 below. A single case may contain more than 1 relevant medical history PT. The most frequently reported medical history PTs referred to rheumatoid arthritis, Crohn's disease and diabetes mellitus.

Table 97: Frequency Distribution of Relevant Medical History PTs in Post-marketing Cases Reported as Booster Dose Involving the Use of Ad26.COV2.S and Reporting Use in Patients With Autoimmune or Inflammatory Disorders

Medical History	Count of Medical History PTs During the Reporting Period[a,b]	Count of Medical History PTs Cumulatively[b]
Rheumatoid arthritis	39	51
Crohn's disease	25	35
Diabetes mellitus	20	41
Ankylosing spondylitis	15	17
Hypothyroidism	15	28
Psoriasis	11	20
Psoriatic arthropathy	11	15
Colitis ulcerative	10	20
Arthritis	9	17
Autoimmune thyroiditis	7	11
Multiple sclerosis	5	6
Hyperthyroidism	4	5
Thyroid disorder	4	11
Uveitis	4	5
Autoimmune disorder	3	6
Myasthenia gravis	3	3
Coeliac disease	2	3
Immune system disorder	2	3
Lichen sclerosus	2	2
Neuropathy peripheral	2	7
Type 1 diabetes mellitus	2	4

Key: PT=Preferred Term

a: The medical history PTs of interest with frequency ≥2 have been presented by decreasing order for the reporting period (25 February 2022 to 24 August 2022).

b: A single case may report more than 1 relevant medical history.

Fatal Post-marketing Booster Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 4 initial, fatal cases reported as booster with 13 fatal events were retrieved. The reported fatal events were COVID-19 pneumonia (n=2), abdominal pain, arthritis, chills, decreased appetite, dysarthria, gait inability, Guillain-Barre syndrome, hyperthermia, malaise, paraesthesia, and vaccination failure (n=1 each).

Literature ICSR

No information was identified that would change the characterisation of use of Ad26.COV2.S in patients with autoimmune and inflammatory conditions.

MAH Conclusion

Based on the evaluation of the cases, and review of safety from other sources, the information is consistent with the information known about use in patients with autoimmune or inflammatory disorders. The Company will continue to closely monitor use of the vaccine in this subpopulation as missing information.

Rapporteur assessment comment:

During the interval reporting period 685 (437 medically confirmed and 248 medically unconfirmed) initial, primary dose cases reporting use in patients with autoimmune or inflammatory disorders were identified reporting a total of 2,712 events Cumulatively, 4,658 (2,490 medically confirmed and 2,168 medically unconfirmed) primary dose cases reporting use in patients with autoimmune or inflammatory disorders were identified, reporting a total of 23,678 events (11,974 serious; 11,704 nonserious). The most frequently reported events (n⩾30) included headache and pyrexia (n=61 each), fatigue (n=51), COVID-19 (n=39), pain (n=38), suspected COVID-19 and vaccination failure (n=31 each), and malaise and myalgia (n=30 each). No new safety concern is detected with primary vaccination or with booster dosing.

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

According to the cRMP (version 4.0; dated 09 December 2021), use in frail patients with comorbidities (eg, chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders) is considered missing information for Ad26.COV2.S.

Primary Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 43 (36 medically confirmed and 7 medically unconfirmed) initial, primary dose cases reporting use in frail patients with comorbidities (eg, COPD, diabetes, chronic neurological disease, cardiovascular disorders) were identified. Of these 43 cases, 21 were serious and 22 were nonserious and reported a total of 75 events (47 serious; 28 nonserious).

Of these 43 primary dose cases received during the interval reporting period, 35 were reported from Janssen Sponsored Clinical Studies and 8 from post-marketing sources (including spontaneous and solicited). No cases were reported from Janssen Supported Clinical Studies. Cumulatively, 205 (137 medically confirmed and 68 medically unconfirmed) primary dose cases reporting use in frail patients with comorbidities (eg, COPD, diabetes, chronic neurological disease, cardiovascular disorders) were identified. Of these cases, 97 were serious and 108 were nonserious and reported a total of 619 events (304 serious; 315 nonserious). Of the 205 cumulative primary dose cases received, 104 were reported from Janssen Sponsored Clinical Studies, 5 from Janssen Supported Clinical Studies, and 96 from post-marketing sources (including spontaneous and solicited cases).

Janssen Sponsored Clinical Studies Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 35 initial, primary dose cases reporting use in frail patients with comorbidities (eg, COPD, diabetes, chronic neurological disease, cardiovascular disorders) were retrieved from Janssen Sponsored Clinical Studies. Of the 35 cases, 25 were from VAC31518COV3001, 8 from VAC31518COV3009, and 2 from VAC31518COV3003. These 35

cases reported 44 events (24 serious; 20 nonserious). Of these 35 cases, the most frequently (n≥5) reported countries/territories of origin were Brazil (n=15), followed by Colombia and the US (n=5 each). These cases concerned 21 males and 14 females. The age range was from 32 to 79 years. The most frequently reported events (≥4) included thrombocytopenia (n=15), deep vein thrombosis (n=7), and pulmonary embolism (n=4). The mean and median TTO were 407.2 and 426.0 days, respectively. The reported outcomes were resolved (n=21), not resolved and resolving (n=9 each), resolved with sequelae (n=3), and fatal (n=2).

Post-marketing Sources (Including Spontaneous and Solicited) Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 8 post-marketing sources (including spontaneous and solicited), initial, primary dose cases reporting use in frail patients with comorbidities (eg, COPD, diabetes, chronic neurological disease, cardiovascular disorders) were retrieved. These 8 post-marketing, initial, primary dose cases reported 31 events (23 serious; 8 nonserious).

Cumulatively, 96 (28 medically confirmed and 68 medically unconfirmed) post-marketing, primary dose cases reporting use in frail patients with comorbidities (eg, COPD, diabetes, chronic neurological disease, cardiovascular disorders) were identified. Of these cases, 49 were serious and 47 were nonserious and reported a total of 482 events (237 serious; 245 nonserious).

For these 8 post-marketing, initial, primary dose cases, the countries/territories of origin were reported the US (n=7) and Germany (n=1). These cases concerned 6 females and 2 males. The age range was from 32 to 70 years.

The frequency distribution of the MedDRA PTs reported in post-marketing, primary dose cases is presented in Table 99 below. A single case may contain more than 1 event. The mean and median TTO

Table 99: Frequency of MedDRA PTs reported in Post-marketing, Primary Dose Cases Reporting Use in Frail Patients With Comorbidities (eg, COPD, Diabetes, Chronic Neurological Disease, Cardiovascular Disorders) With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Alopecia	0	1	0	2
Arthralgia	1	0	2	5
Arthritis infective	1	0	1	0
Asthenia	0	1	0	4
Blood test abnormal	1	0	1	0
Cataract	1	0	1	0
Chills	0	1	0	11
Chondrocalcinosis pyrophosphate	1	0	1	0
Compartment syndrome	1	0	1	0
Death	1	0	5	0
Decubitus ulcer	1	0	1	0
Exposure during pregnancy	0	1	0	1
Eye disorder	1	0	1	0
Eye infection	1	0	1	0
Fall	0	1	1	3
Haematochezia	1	0	1	0
Haemorrhage	1	0	2	0
Hepatic vascular thrombosis	1	0	1	0
Ill-defined disorder	1	0	1	0
Illness	0	1	0	2
Injury	0	1	0	1
Knee operation	1	0	1	0
Memory impairment	0	1	0	2
Muscle contracture	1	0	1	0
Musculoskeletal disorder	1	0	1	0
Musculoskeletal stiffness	1	0	1	0
Myocardial infarction	1	0	1	0
Pain	1	0	2	8
Sepsis	1	0	1	0
Speech disorder	1	0	3	1
Thrombosis	1	0	7	0

Key: COPD=Chronic Obstructive Pulmonary Disorder; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term

a: A single case may report more than 1 event.

were 56.0 and 26.5 days, respectively. Where reported (n=12), the outcomes were not resolved and resolving (n=4 each), resolved (n=3), and fatal (n=1). The frequency distribution of relevant medical history PTs reported in the 8 cases is presented in Table 100 below.

Table 100: Frequency Distribution of Relevant Medical History PTs Involving the Use of Ad26.COV2.S and Reporting Use in Frail Patients With Comorbidities (eg, COPD, Diabetes, Chronic Neurological Disease, Cardiovascular Disorders)

Medical History	Count of Medical History PTs During the Reporting Period[a]	Count of Medical History PTs Cumulatively
Disability	3	31
Wheelchair user	2	13
Bedridden	1	11
Exercise lack of	1	23
Walking aid user	1	6

Key: COPD=Chronic Obstructive Pulmonary Disorder; PT=Preferred Term

a: The medical history PTs of interest have been presented by decreasing order for the reporting period (25 February 2022 to 24 August 2022).

Fatal Post-marketing Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 1 post-marketing, initial, primary dose fatal case with 1 fatal event was retrieved. The reported fatal event was death which occurred in a 67-year-old female with a past medical history of tobacco use, drug abuse, hepatitis C, oophroectomy, and benign ovarian tumour, and a concurrent conditions of rheumatoid arthritis, fibromyalgia, physical disability, liver disorder, and bedridden. The cause of death was not provided. The patient was hospitalised approximately 8 months post-vaccination for liver thrombosis. It was reported that the patient's "toxins" were high. Subsequently, the patient died 297 days post-vaccination. An autopsy was not performed. This case was medically unconfirmed.

Booster Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 14 (10 medically confirmed and 4 medically unconfirmed) initial cases reported as booster were identified. There were 2 serious and 12 nonserious cases and reported a total of 33 events (10 serious; 23 nonserious). Of these cases, 11 were homologous and 3 were heterologous. Of these 14 cases reported as booster during the interval, 9 were reported from Janssen Sponsored Clinical Studies and 5 from post-marketing sources (including spontaneous and solicited). No cases were reported from Janssen Supported Clinical Studies.

Cumulatively, 40 (34 medically confirmed and 6 medically unconfirmed) cases reported as booster were identified. Of these cases, 4 were serious and 36 were nonserious and reported a total of 65 events (12 serious; 53 nonserious). Of these cases, 37 were homologous and 3 were heterologous.

Of the 40 cumulative cases reported as booster, 33 were reported from Janssen Sponsored Clinical Studies and 7 from post-marketing sources (including spontaneous and solicited cases). No cases were reported from Janssen Supported Clinical Studies.

Janssen Sponsored Clinical Studies Booster Dose Cases

During the interval reporting period of 25 February 2022 to 24 August 2022, 9 initial cases reported as booster were retrieved from a Janssen Sponsored Clinical Study. All 9 cases were from VAC31518COV3001. These 9 cases reported 10 nonserious events. The reported countries/territories of origin in these 9 cases were the US (n=4), followed by Brazil (n=3), and Colombia and South Africa (n=1 each). These cases concerned 6 males and 3 females. None of the cases reported an age.

The reported events included thrombocytopenia (n=8) and hyperferritinaemia and platelet count decreased (n=1 each). The mean and median TTO were 122.5 and 28 days, respectively. Where reported (n=7), the outcome was resolving (n=4) and resolved (n=3).

Post-marketing Sources (Including Spontaneous and Solicited) Booster Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 5 post-marketing sources (including spontaneous and solicited), initial cases reported as booster were retrieved. These 5 post-marketing, booster dose cases reported 23 events (10 serious; 13 nonserious). Cumulatively, 7 (1 medically confirmed and 6 medically unconfirmed) post-marketing cases reported as booster were identified. Of these cases, 3 were serious and 4 were nonserious and reported a total of 31 events (11 serious; 20 nonserious).

Of these 5 post-marketing, initial cases reported as booster, the reported countries/territories of origin were the US (n=3), followed by Austria and Brazil (n=1 each). These cases concerned 3 males and 2 females. The age range was from 48 to 79 years. The frequency distribution of the MedDRA PTs reported in post-marketing cases reported as booster is presented in Table 102 below. A single case may contain more than 1 event.

Table 102: Frequency of MedDRA PTs reported in Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Use in Frail Patients With Comorbidities (eg, COPD, Diabetes, Chronic Neurological Disease, Cardiovascular Disorders)

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Deep vein thrombosis	2	0	2	0
Acute respiratory distress syndrome	1	0	1	0
Chest pain	0	1	0	1
COVID-19 pneumonia	1	0	1	0
Decreased appetite	0	1	0	1
Dependence on respirator	1	0	1	0
Dizziness	0	1	0	2
Dysgeusia	0	1	0	1
Dyspnoea	0	1	0	1
Gait disturbance	1	0	1	0
Hyperhidrosis	0	1	0	1
Insomnia	0	1	0	1
Off label use	0	1	0	1
Palpitations	0	1	0	1
Performance status decreased	1	0	1	0
Pulmonary embolism	1	0	1	0
Rash	0	1	0	1
Subdural haematoma	1	0	1	0
Suspected COVID-19	0	1	0	1
Taste disorder	0	1	0	1
Vaccination failure	1	0	1	0
Vomiting	0	1	0	1

Key: COPD=Chronic Obstructive Pulmonary Disorder; COVID-19=Coronavirus Disease-2019; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term

a: The MedDRA PTs have been sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event.

The most frequently reported event was deep vein thrombosis (n=2). The mean and median TTO were 106.4 and 89.5 days, respectively. Where reported (n=13), the outcomes were resolved (n=8), not resolved (n=4), and fatal (n=1). The frequency distribution of relevant medical history PTs reported in the 5 cases is presented in Table 103 below. A single case may contain more than 1 relevant medical history PT.

Table 103: Frequency Distribution of Relevant Medical History PTs Involving the Use of Ad26.COV2.S and Reporting Use in Frail Patients With Comorbidities (eg, COPD, Diabetes, Chronic Neurological Disease, Cardiovascular Disorders)

Medical History	Count of Medical History PTs During the Reporting Period[a,b]	Count of Medical History PTs Cumulatively[b]
Wheelchair user	2	2
Anorexia nervosa	1	1
Bedridden	1	1
Housebound	1	1
Walking aid user	1	2

Key: COPD=Chronic Obstructive Pulmonary Disorder; PT=Preferred Term

a: The medical history PTs of interest have been presented by decreasing order for the reporting period (25 February 2022 to 24 August 2022).

b: A single case may report more than 1 relevant medical history PT.

Fatal Post-marketing Booster Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 1 initial, fatal case reported as booster with 1 fatal event was retrieved. The reported fatal event was acute respiratory distress syndrome. This case concerned a 68-year-old male prison inmate with a history of cervical and supraspinal laminectomy and concurrent conditions of hypertension, mobility decreased, obesity, and wheelchair dependent who experienced shortness of breath and difficulty breathing approximately 79 days following a booster dose of Ad26.COV2.S. The patient was hospitalized due to hypoxia and was placed on mechanical ventilation. Acute respiratory failure was diagnosed as well as a right lower leg deep vein thrombosis and pulmonary embolism. Subsequently, the patient was diagnosed with a subdural hematoma. The patient's clinical course continued to deteriorate as the patient was diagnosed with bilateral pneumonia and tested positive for COVID-19 infection. The patient died from respiratory failure secondary to acute respiratory distress syndrome approximately 138 days following the booster dose of Ad26.COV2.S. It was unknown if an autopsy was performed.

Literature ICSR

No ICSR literature cases were received during the reporting period of 25 February 2022 to 24 August 2022.

MAH Conclusion

Based on the evaluation of the cases, and review of safety from other sources, the information is consistent with the information known about use in frail patients with comorbidities (eg, COPD, diabetes, chronic neurological disease, cardiovascular disorders). The Company will continue to closely monitor use in frail patients with comorbidities (eg, COPD, diabetes, chronic neurological disease, cardiovascular disorders) as a missing information.

Rapporteur assessment comment:

No new safety concern is detected with frail patients.

Interaction With Other Vaccines

Information on interaction with other vaccines has been presented in Section "Use With Concomitant Vaccination".

Long-term Safety

According to the cRMP (version 4.0; dated 09 December 2021), long-term safety is considered missing information with the use of Ad26.COV2.S.

Primary Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 199 (160 medically confirmed and 39 medically unconfirmed) initial, primary dose cases with a latency of ≥6 months after the primary vaccination were identified. Of these 199 cases, 163 were serious and 36 were nonserious and reported a total of 316 events (187 serious; 129 nonserious).

Of these 199 primary dose cases received during the interval reporting period, 27 were reported from Janssen Sponsored Clinical Studies, 115 from Janssen Supported Clinical Studies, and 57 from post-marketing sources (including spontaneous and solicited).

Cumulatively, 437 (268 medically confirmed and 169 medically unconfirmed) primary dose cases with a latency of ≥6 months after the primary vaccination were identified. Of these cases, 264 were serious and 173 were nonserious and reported a total of 794 events (316 serious; 478 nonserious). Of the 437 cumulative primary dose cases received, 66 were reported from Janssen Sponsored Clinical Studies, 162 from Janssen Supported Clinical Studies, and 209 from post-marketing sources (including spontaneous and solicited cases).

Janssen Sponsored Clinical Studies Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 27 initial, primary dose cases with a latency of ≥6 months after the primary vaccination were retrieved from Janssen Sponsored Clinical Studies. Of the 27 cases, 24 were from VAC31518COV3001, 2 from VAC31518COV1001, and 1 from VAC31518COV3009. These 27 cases reported 32 events (31 serious; 1 nonserious). Of these 27 cases, the most frequently reported countries/territories of origin (n≥9) were the US (n=11), followed by South Africa (n=9). These cases concerned 15 females and 12 males. The age range was from 30 to 84 years. The events (n≥2) included cerebrovascular accident, diabetic ketoacidosis, head injury, and thrombocytopenia (n=2 each). The mean and median TTO were 458.0 and 448.5 days, respectively. The outcomes were fatal (n=10), resolved (n=9), resolving (n=7), and not resolved and resolved with sequelae (n=3 each).

Janssen Supported Clinical Studies Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 115 initial, primary dose cases with a latency of ≥6 months after the primary vaccination were retrieved from Janssen Supported Clinical Studies. Of the 115 cases, 112 were from VAC31518COV3021 and 3 from VAC31518COV3012. These 115 cases reported 116 events (115 serious; 1 nonserious). The country/territory of origin in all 115 cases was South Africa. These cases concerned 86 females and 29 males. The age range was from 24 to 89 years.

The events (n>100) included COVID-19 (n=114). The mean and median TTO were 368.2 and 375 days, respectively. Where reported (n=115), the outcomes were resolved (n=108), fatal (n=6),and resolving (n=1).

Post-marketing Sources (Including Spontaneous and Solicited) Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 57 post-marketing sources (including spontaneous and solicited), initial, primary dose cases with a latency of≥6 months after the primary vaccination were retrieved. These 57 post-marketing, initial, primary dose cases reported 168 events (41 serious; 127 nonserious).

Cumulatively, 209 (40 medically confirmed and 169 medically unconfirmed) post-marketing, primary dose cases with a latency of ≥6 months after the primary vaccination were identified. Of these cases, 53 were serious and 156 were nonserious and reported a total of 546 events (96 serious; 450 nonserious).

Of these 57 post-marketing, initial, primary dose cases, the most frequently reported countries/territories of origin (n≥8) were the US (n=20), followed by Germany (n=8). These cases concerned 31 females, 21 males, and 5 did not report sex. The age range was from 25 to 76 years. The frequency distribution of the

MedDRA PTs reported in post-marketing, primary dose cases is presented in Table 105 below. A single case may contain more than 1 event.

Table 105: Frequency of MedDRA PTs in Post-marketing, Primary Dose Cases Reporting Long-term Safety With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Headache	0	5	1	32
Off label use	0	5	0	10
Pyrexia	2	3	5	37

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

a: The MedDRA PTs with a frequency ≥5 have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event.

The events (n≥5) included headache, off label use, and pyrexia (n=5 each). The mean and median TTO were 699.3 and 59.5 days, respectively. Where reported (n=98), the outcomes were not resolved (n=66), resolved (n=17), resolving (n=14), and fatal (n=1).

Fatal Post-marketing Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 1 post-marketing, initial, primary dose case with a fatal outcome was identified in the scientific literature. This case concerned high levels of aspartate aminotransferase (AST) observed in hospitalised patients while being treated for the SARS-COV2 infection. The authors concluded that an increased AST level was an independent factor of death in the study population (n=250 patients with primary vaccination with Ad26.COV2.S) for which no specific medical history, concurrent conditions, concomitant medications, treatments, causes of death, or autopsy results were reported.

Booster Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 32 (8 medically

confirmed and 24 medically unconfirmed) initial cases reported as booster were identified. There were 12 serious and 20 nonserious cases and reported a total of 86 events (15 serious; 71 nonserious). Of these cases, 19 were homologous and 13 were heterologous. Of these 32 cases reported as booster during the interval, 1 was reported from a Janssen Sponsored Clinical Study, 2 from Janssen Supported Clinical Studies, and 29 from post-marketing sources (including spontaneous and solicited).

Cumulatively, 49 (11 medically confirmed and 38 medically unconfirmed) cases reported as booster were identified. Of these cases, 19 were serious and 30 were nonserious and reported a total of 153 events (29 serious; 124 nonserious). Of these cases, 30 were homologous and 19 were heterologous.

Of the 49 cumulative cases reported as booster, 1 was reported from a Janssen Sponsored Clinical Study, 4 from Janssen Supported Clinical Studies, and 44 from post-marketing sources (including spontaneous and solicited cases).

Janssen Sponsored Clinical Studies Booster Dose Cases

During the interval reporting period of 25 February 2022 to 24 August 2022, 1 initial case reported as booster was retrieved from a Janssen Sponsored Clinical Study. This case was reported from VAC31518COV3001 and concerned a 70-year-old male from [redacted] who experienced the serious events

of diverticulitis, haematochezia, and melaena. The mean and median TTO were 391.7 and 398.0 days, respectively. The outcomes were reported as resolved (n=2) and resolved with sequelae (n=1).

Janssen Supported Clinical Studies Booster Dose Cases

During the interval reporting period of 25 February 2022 to 24 August 2022, 2 initial cases reported as booster were retrieved from Janssen Supported Clinical Studies. Both cases were from VAC31518COV3021 and reported 2 serious events. The reported country/territory of origin was South Africa for both cases. Both cases concerned females. The age was reported as 45 and 58.8 years.

The events included COVID-19 (n=2). The mean and median TTO was 371 days. The outcomes for the reported events were fatal (n=1) and resolved (n=1).

Post-marketing Sources (Including Spontaneous and Solicited) Booster Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 29 post-marketing sources (including spontaneous and solicited), initial cases reported as booster were retrieved. These 29 post-marketing, booster dose cases reported 81 events (10 serious; 71 nonserious). Cumulatively, 44 (6 medically confirmed and 38 medically unconfirmed) post-marketing cases reported as booster were identified. Of these cases, 14 were serious and 30 were nonserious and reported a total of 146 events (22 serious; 124 nonserious).

Of these 29 post-marketing, initial cases reported as booster, the most frequently reported countries/territories of origin (n≥6) were the US (n=12), followed by Brazil (n=6). These cases

concerned 19 females, 7 males, and 3 did not report sex. The age range was from 18 to 80 years. The frequency distribution of the MedDRA PTs reported in post-marketing cases reported as booster is presented in Table 107 below. A single case may contain more than 1 event.

The events (n≥5) included off label use (n=9), inappropriate schedule of product administration (n=6), and COVID-19 (n=5). The mean and median TTO were 148.4 and 31 days respectively. Where reported (n=26), the outcomes were not resolved (n=13), resolved (n=10), and resolving (n=3).

Table 107: Frequency of MedDRA PTs in Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Long-term Safety

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Off label use	0	9	0	17
Inappropriate schedule of product administration	0	6	0	14
COVID-19	0	5	0	7

Key: COVID-19: Coronavirus Disease-2019; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term

a: The MedDRA PTs with a frequency ≥5 have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event.

Fatal Post-marketing Booster Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 1 post-marketing case from Germany was retrieved which concerned an 18-year-old (sex unspecified) who died at an unspecified time following initial vaccination with Ad26.COV2.S and subsequent booster vaccines: elasomeran (dose 2), CHADOX 1 NCOV-19 (dose 3), and tozinameran (dose 4). This case lacked relevant details concerning the patient's medical history/concurrent conditions, clinical course/treatment, concomitant medications,

and cause of death. It was unknown if an autopsy was performed or if AEs following immunisation occurred with the above-named COVID-19 vaccines.

Literature ICSR

No information was identified that would change the characterisation of risk.

MAH Discussion

Review of cases including demographics, concurrent conditions/medical history, concomitant medications, seriousness, and outcome received during the period covered by this report did not identify evidence suggestive of missing information of long-term safety being causally associated with Ad26.COV2.S.

MAH conclusion

Based on the evaluation of the cases, and review of safety from other sources, the information is consistent with the information known about long-term safety. The Company will continue to closely monitor long-term safety as missing information.

Rapporteur assessment comment:
No new safety concerns are detected in association with long time safety.

2.3.1. Adverse Events of Special Interest

Cardiac Disorders

Cardiac Inflammatory Disorder, Including Myocarditis and Pericarditis

Cardiac inflammatory disorders, including myocarditis and pericarditis, is listed as an AESI in the cRMP, EU RMP, and the US Pharmacovigilance Plan (PVP).

Primary Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 58 (33 medically confirmed and 25 medically unconfirmed) initial, primary dose cases reporting cardiac inflammatory disorders, including myocarditis and pericarditis, were identified. All 58 cases were serious and reported a total of 59 serious EOI. Of these 58 primary dose cases received during the interval reporting period, 3 were reported from Janssen Sponsored Clinical Studies and 55 from post-marketing sources (including spontaneous and solicited cases). No cases were reported from Janssen Supported Clinical Studies. Cumulatively, 411 (244 medically confirmed and 167 medically unconfirmed) primary dose cases reporting cardiac inflammatory disorders, including myocarditis and pericarditis, were identified. All 411 cases were serious and reported a total of 430 serious EOI. Of the 411 cumulative primary dose cases received, 6 were reported from Janssen Sponsored Clinical Studies, 2 from Janssen Supported Clinical Studies, and 403 from post-marketing sources (including spontaneous and solicited cases).

Janssen Sponsored Clinical Studies Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 3 initial, primary dose cases reporting cardiac inflammatory disorders, including myocarditis and pericarditis, were retrieved from Janssen Sponsored Clinical Studies. Of the 3 cases, 1 each was reported from VAC31518COV3001, VAC31518COV3003, and VAC31518COV3009. These 3 cases reported 3 serious EOI. Of these 3 cases, the most frequently reported country/territory of origin (n≥2) was Brazil (n=2). All 3 cases concerned

males. The age range was from 29 to 45 years. The EOI included myocarditis (n=2) and myopericarditis (n=1). The mean and median TTO was 279.5 days. The outcomes were reported as resolved (n=2) and resolving (n=1).

Post-marketing Sources (Including Spontaneous and Solicited) Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 55 post-marketing sources (including spontaneous and solicited), initial, primary dose cases reporting cardiac inflammatory disorders, including myocarditis and pericarditis, were retrieved. These 55 post-marketing, initial, primary dose cases reported 56 serious EOI.

Cumulatively, 403 (236 medically confirmed and 167 medically unconfirmed) post-marketing, primary dose cases reporting cardiac inflammatory disorders, including myocarditis and pericarditis, were identified. All 403 cases were serious and reported a total of 422 serious EOI. Of these 55 post-marketing, initial, primary dose cases, the most frequently reported countries/territories of origin (n≥14) were the US (n=19), followed by Germany (n=14). These cases concerned 32 males, 17 females, and 6 did not report sex. The age range was from 18 to 68 years. The EOI (n≥6) included myocarditis (n=33), pericarditis (n=16), and myopericarditis (n=6). The mean and median TTO were 54.6 days and 11.0 days respectively. Where reported (n=42), the outcomes were not resolved (n=20), resolving (n=7), resolved and resolved with sequelae (n=6 each), and fatal (n=3).

Table 109: Frequency of MedDRA PTs of Interest in Post-marketing, Primary Dose Cases Reporting Cardiac Inflammatory Disorders, Including Myocarditis And Pericarditis With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Myocarditis	33	0	201	0
Pericarditis	16	0	186	0
Myopericarditis	6	0	29	0
Giant cell myocarditis	1	0	1	0

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

a: The MedDRA PTs of interest have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event of interest.

Fatal Post-marketing Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 3 post-marketing, initial, primary dose fatal cases with 3 fatal EOI were retrieved. The fatal EOI was myocarditis in all 3 cases.

Two fatal cases reported a TTO within the risk window of 42 days. Of the 2 cases, 1 is medically confirmed and 1 is medically unconfirmed. Patient age is reported in 1 case. A 62-year-old male, with the TTO reported as 7 days post-vaccination in 1 case, and 40 days post-vaccination in the remaining case. The cause of death in these cases was reported as unspecified cause (n=1), and myocarditis, cardiac failure congestive (n=1). Both cases lacked essential information (medical history/concurrent conditions, autopsy report, clinical course details including diagnostic/laboratory workup, and concomitant medications) precluding any meaningful medical assessment.

One medically unconfirmed case reported the TTO outside of the risk window of 42 days. A 57-year-old female had a TTO reported as 73 days post-vaccination. The cause of death was reported as myocarditis. The case also lacked essential information (medical history/concurrent conditions, autopsy report, clinical course details including diagnostic/laboratory workup, and concomitant medications) precluding any meaningful medical assessment.

Booster Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 19 (6 medically confirmed and 13 medically unconfirmed) initial cases reported as booster were identified. All 19 cases were serious and reported a total of 20 serious EOI. Of these cases, 10 were heterologous and 9 were homologous. Of these 19 cases reported as booster during the interval, 1 was reported from a Janssen Supported Clinical Study and 18 from post-marketing sources (including spontaneous and solicited). No cases were reported from Janssen Sponsored Clinical Studies.

Cumulatively, 24 (7 medically confirmed and 17 medically unconfirmed) cases reported as booster were identified. All 24 cases were serious and reported a total of 27 serious EOI. Of these cases, 12 were heterologous and 12 were homologous.

Of the 24 cumulative booster dose cases received, 1 was reported from a Janssen Supported Clinical Study and 23 from post-marketing sources (including spontaneous and solicited cases). No cases were reported from Janssen Sponsored Clinical Studies.

Janssen Supported Clinical Studies Booster Dose Cases

During the interval reporting period of 25 February 2022 to 24 August 2022, 1 initial case reported as booster was retrieved from a Janssen Supported Clinical Study. This case was reported from VAC31518COV3021 and concerned a 23-year-old female from South Africa, who experienced a serious EOI of pericarditis. The TTO was reported as 3 days from the first dose, and the outcome was reported as resolved.

Post-marketing Sources (Including Spontaneous and Solicited) Booster Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 18 post-marketing sources (including spontaneous and solicited), initial cases reported as booster were retrieved. These 18 post-marketing booster dose cases reported 19 serious EOI. Cumulatively, 23 (6 medically confirmed and 17 medically unconfirmed) post-marketing cases reported as booster were identified. All 23 cases were serious and reported a total of 26 serious EOI.

Table 111: Frequency of MedDRA PTs of Interest in Post-Marketing Cases Reported as Booster Dose With the Use of Ad26.COV2.S and Reporting Cardiac Inflammatory Disorders, Including Myocarditis And Pericarditis

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Myocarditis	11	0	17	0
Pericarditis	8	0	9	0

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

a: The MedDRA PTs of interest have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022).

Of these 18 post-marketing, initial cases reported as booster, the most frequently reported countries/territories of origin (n≥5) were Germany (n=6), followed by the US (n=5). These cases concerned 13 males and 5 females. The age range was from 21 to 66 years. The frequency distribution of the MedDRA PTs of interest reported in post-marketing cases The EOI included myocarditis (n=11) and pericarditis (n=8). The mean and median TTO were 50.5 and 11.0 days, respectively. Where reported (n=12), the outcomes were not resolved and resolved (n=5 each) and resolving (n=2).

There were no fatal cases reported as booster which were retrieved from the search of the Company global safety database during the interval reporting period of 25 February 2022 to 24 August 2022.

Literature ICSR

No information was identified that would change the characterisation of risk.

O/E Analysis Results

Table 112: Myocarditis: Restricted O/E and Sensitivity Analysis Results (Cumulative Through 24 August 2022)

Restricted 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	Female	18 to 29	4.00	2.25	(0.61, 5.75)	16.33	(4.45, 41.81)
		30 to 39	4.00	1.25	(0.34, 3.19)	5.57	(1.52, 14.27)
		40 to 49	4.00	1.16	(0.32, 2.98)	4.63	(1.26, 11.86)
		50 to 64	4.00	0.82	(0.22, 2.09)	3.45	(0.94, 8.84)
		65 to 74	4.00	0.74	(0.20, 1.88)	2.59	(0.71, 6.64)
		≥75	0.00	0.00	(0.00, 1.40)	0.00	(0.00, 5.41)
	Male	18 to 29	15.00	1.11	(0.62, 1.83)	3.59	(2.01, 5.92)
		30 to 39	4.00	0.46	(0.13, 1.18)	1.50	(0.41, 3.85)
		40 to 49	5.00	0.94	(0.30, 2.18)	3.22	(1.05, 7.53)
		50 to 64	4.00	0.43	(0.12, 1.11)	1.59	(0.43, 4.06)
		65 to 74	1.00	0.24	(0.01, 1.32)	0.91	(0.02, 5.06)
EU	Female	18 to 29	4.00	2.14	(0.58, 5.49)	15.57	(4.24, 39.86)
		30 to 39	2.00	0.55	(0.07, 1.97)	2.44	(0.30, 8.81)
		40 to 49	7.00	1.73	(0.70, 3.57)	6.88	(2.77, 14.19)
		50 to 64	5.00	0.97	(0.31, 2.26)	4.08	(1.33, 9.53)
		65 to 74	2.00	0.44	(0.05, 1.60)	1.56	(0.19, 5.63)
	Male	18 to 29	31.00	2.15	(1.46, 3.04)	6.96	(4.73, 9.87)
		30 to 39	12.00	1.22	(0.63, 2.12)	3.98	(2.05, 6.95)
		40 to 49	5.00	0.79	(0.26, 1.85)	2.73	(0.89, 6.38)
		50 to 64	14.00	1.45	(0.79, 2.44)	5.31	(2.90, 8.90)
		65 to 74	2.00	0.59	(0.07, 2.14)	2.26	(0.27, 8.18)
		≥75	1.00	0.54	(0.01, 3.01)	2.23	(0.06, 12.40)

Key: CI=Confidence Interval; EOI=Event(s) of Interest; EU=European Union; LB=Lower Bound; O/E=Observed versus Expected; PE=Point Estimate; RP=Reporting Percentage; US=United States

a: Counts included EOI (from valid cases) that occurred within the risk window (Day: 1 to 42) only.

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

The US restricted sensitivity analysis showed an O/E ratio of>1 for all female and male age groups concerned except the female ≥75 age group and the male 65 to 74 age group. Of these, the O/E ratio was statistically significant above 1 (lower bound of 95% confidence interval >1) for the female 18 to 29, 30 to 39, and 40 to 49, and male 18 to 29 and 40 to 49 age groups only. The EU restricted sensitivity analysis showed an O/E ratio of >1 for all female and male age groups concerned. Of these, the O/E ratio was statistically significant above 1 (lower bound of 95% confidence interval >1) for the female 18 to 29, 40 to 49, and 50 to 64 age groups, and male 18 to 29, 30 to 39, and 50 to 64 age groups. A restricted analysis, to include sensitivity analysis, was not performed for the EU 65 to 74 age group in the previous PBRER with DLP 24 February 2022. At the time of the current PBRER DLP, the EU 65 to 74 age group restricted sensitivity O/E ratio was >1. This O/E ratio was not statistically significant above 1 (lower bound of 95% confidence interval <1).

Pericarditis

Results of the restricted O/E and sensitivity analysis are presented in Table 113.

Table 113: Pericarditis: Restricted O/E and Sensitivity Analysis Results (Cumulative Through 24 August 2022)

Restricted 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	Female	30 to 39	8.00	0.36	(0.16, 0.72)	0.97	(0.42, 1.91)

Key: CI=Confidence Interval; EOI=Event(s) of Interest; EU=European Union; LB=Lower Bound; O/E=Observed versus Expected; PE=Point Estimate; RP=Reporting Percentage; US=United States

a: Counts included EOI (from valid cases) that occurred within the risk window (Day: 1 to 42) only.

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

The US restricted sensitivity analysis showed an O/E ratio of <1 for the female 30 to 39 age group. Results of the US and EU O/E analysis (both broad and restricted, where applicable) are provided in Appendix 7.2, this includes cumulative exposure, expected counts and background incidence rates.

MAH conclusion

Based on the evaluation of the cases, and review of safety from other sources, the information is consistent with the information known about cardiac inflammatory disorders, including myocarditis and pericarditis. The Company will continue to closely monitor cardiac inflammatory disorders, including myocarditis and pericarditis, as an AESI.

Rapporteur assessment comment:

Myocarditis and Pericarditis have been in-depth analysed in the MSSRs 7-9. The PRAC considered that the available data did not support causal association for the AD26.COV2.S vaccine and should be followed through routine pharmacovigilance activities. As seen in earlier reports O/E analyses show disproportionality in some of the sensitivity analysis for myocarditis. 18 cases in the interval and 23 cases of cardiac inflammatory diseases were reported after booster vaccination. No new safety information of particular concern is identified during the reporting period for this PSUR. A close monitoring of the term in the upcoming PSURs is supported.

On 17 February 2023, the MAH informed EMA that the U.S. FDA had on 14 Feb 2023 requested to update the JCOVDEN EUA fact sheet to include new W&P for myocarditis and pericarditis. The MAH also stated that based on the totality of safety data available, J there is at present insufficient evidence to establish a causal association between Ad26.COV2.S and the occurrence of cardiac inflammatory disorders (incl. Myocarditis and Pericarditis). The MAH continues to monitor both conditions as AESIs as defined in the RMP and will provide an updated and detailed analysis in the upcoming PSUR. Given previous thorough assessments, this is considered sufficient.

A further update in the form of an ESI was submitted by the MAH on 31 March 2023; see late breaking information (Section 1.3.7) and Section 2 Assessment conclusions and actions.

Cardiomyopathy

Cardiomyopathy is listed as an AESI in the cRMP, EU RMP, and the US PVP.

Primary Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 17 (12 medically confirmed and 5 medically unconfirmed) initial, primary dose cases reporting cardiomyopathy were identified. All 17 cases were serious and reported a total of 18 serious EOI. Of these 17 primary dose cases received during the interval reporting period, 1 was reported from a Janssen Sponsored Clinical Study and 16 from post-marketing spontaneous sources. No cases were reported from Janssen Supported Clinical Studies. Cumulatively, 74 (49 medically confirmed and 25 medically unconfirmed) primary dose cases reporting cardiomyopathy were identified. All 74 cases were serious and reported a total of 82 EOI (79 serious; 3 nonserious). Of the 74 cumulative primary dose cases received, 4 were reported from Janssen Sponsored Clinical Studies and 70 from post-marketing spontaneous sources. No cases were reported from Janssen Supported Clinical Studies.

Janssen Sponsored Clinical Studies Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 1 initial, primary dose case reporting cardiomyopathy was retrieved from a Janssen Sponsored Clinical Study. This case was reported from VAC31518COV3009 and concerned a 45-year-old male from [redacted] who experienced a serious EOI of myocardial fibrosis. The TTO was reported as 90.0 days from the first dose, and the outcome was not resolved.

Post-marketing Sources (Including Spontaneous and Solicited) Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 16 post-marketing sources (including spontaneous and solicited), initial, primary dose cases reporting cardiomyopathy were retrieved. These 16 post-marketing, initial, primary dose cases reported 17 serious EOI.

Cumulatively, 70 (45 medically confirmed and 25 medically unconfirmed) post-marketing, primary dose cases reporting cardiomyopathy were identified. All 70 cases were serious and reported a total of 78 EOI (75 serious; 3 nonserious).

Of these 16 post-marketing, initial, primary dose cases, the most frequently reported countries/territories of origin (n≥6) were Germany and the US (n=6 each). These cases concerned 14 males and 2 females. The age range was from 19 to 70 years.

The frequency distribution of the MedDRA PTs of interest reported in post-marketing, primary dose cases is presented in Table 115 below. A single case may contain more than 1 EOI.

The EOI (n≥3) included cardiomyopathy (n=5), and congestive cardiomyopathy and ejection fraction decreased (n=3 each). The mean and median TTO were 91.6 and 13.0 days, respectively. Where reported (n=13), the outcomes were not resolved (n=4), resolving (n=3), and fatal, resolved and resolved with sequelae (n=2 each).

Table 115: Frequency of MedDRA PTs of Interest in Post-marketing, Primary Dose Cases Reporting Cardiomyopathy With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Cardiomyopathy	5	0	21	0
Congestive cardiomyopathy	3	0	9	0
Ejection fraction decreased	3	0	20	2

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

a: The MedDRA PTs of interest with a frequency ≥3 have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event of interest.

Fatal Post-marketing Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 3 post-marketing, initial, primary dose fatal cases with 2 fatal EOI were retrieved. The fatal EOI was hypertrophic cardiomyopathy in both cases. One case reported a TTO outside of the risk window of 30 days and for 1 case the TTO was not reported.

The case occurring outside the risk window was medically unconfirmed. This case was received via the Regulatory Authority (EVHUMAN Vaccines, [redacted]) and concerned a 70-year-old male who experienced hypertrophic cardiomyopathy, and pulmonary thromboembolism on Day 202 post-vaccination and died 10 days later due to these events. No further details were reported. It was unspecified if an autopsy was performed. The lack of available information (specifically medical history/concurrent conditions, cosuspect/concomitant medications, and laboratory and diagnostic test results) precludes a meaningful medical assessment.

The second case was medically confirmed and concerned a 69-year-old male with no past medical history or concomitant conditions. Nine days after receiving Ad26.COV2.S, the patient experienced cerebral venous thrombosis, MI, coronary thrombosis, cerebral venous sinus thrombosis, severe coronary sclerosis, anti-pf4 antibodies, and cardiac hypertrophy. An unspecified duration later, the patient died of AMI. The outcome of cardiac hypertrophy and other events was not reported. An autopsy was performed, and the findings included cerebral venous sinus thrombosis (CVST) with non-significant neuropathologic changes, coronary sclerosis, coronary thrombosis, cardiac hypertrophy, fresh MI and anti-PF4 antibodies. The myocardial histology showed fresh myocardial ischaemia, while the cerebral tissue did not show any significant alteration.

The third case was medically unconfirmed and concerned a 19-year-old male who experienced hypertrophic cardiomyopathy within a month after receiving Ad26.COV2.S and died. The patient's family reported that autopsy results found hypertrophic cardiomyopathy as the cause of death while gene test results did not show hypertrophic cardiomyopathy as the cause. This case lacks essential information regarding the patient's medical history, concomitant medication, the clinical course of events, diagnostic and laboratory results precluding any meaningful medical assessment.

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

Booster Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 1 initial case reported as booster was identified. This case was medically unconfirmed, serious and reported 1 serious EOI. This case was heterologous and was reported from a post-marketing spontaneous source. No cases were reported from Janssen Sponsored Clinical Studies or Janssen Supported Clinical Studies. Cumulatively, 4 (1 medically confirmed and 3 medically unconfirmed) cases reported as booster were identified. All 4 cases were serious and reported a total of 4 serious EOI. Of these cases, 3 were heterologous and 1 was homologous. All 4 cumulative booster dose cases received were reported from post-marketing spontaneous sources. No cases were reported from Janssen Sponsored Clinical Studies or Janssen Supported Clinical Studies.

Post-marketing Sources (Including Spontaneous and Solicited) Booster Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 1 initial case reported as booster was retrieved from a post-marketing spontaneous source. This case concerned a 50-year-old male from [redacted] who experienced a serious EOI of ejection fraction decreased. The TTO was 224 days from the first dose and the outcome was resolving.

Cumulatively, 4 (1 medically confirmed and 3 medically unconfirmed) post-marketing cases reported as booster were identified. All cases were serious and reported a total of 4 serious EOI.

There were no fatal cases reported as booster which were retrieved from the search of the Company global safety database during the interval reporting period of 25 February 2022 to 24 August 2022.

Literature ICSR

No information was identified that would change the characterisation of risk.

MAH Discussion

The majority of the cases reported during the interval were reported from the US and Germany and were males (87.5%). The median age was 56 years. Overall, no specific patterns among cases reporting cardiomyopathy were identified.

O/E Analysis Results

Table 116: Cardiomyopathies: Restricted O/E and Sensitivity Analysis Results (Cumulative Through 24 August 2022)

Restricted 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	14.00	3.13	(1.71, 5.26)	6.43	(3.52, 10.79)
	≥60	9.00	0.70	(0.32, 1.33)	2.36	(1.08, 4.48)
EU	18 to 59	7.00	1.37	(0.55, 2.82)	2.81	(1.13, 5.79)
	≥60	4.00	0.39	(0.11, 1.01)	1.33	(0.36, 3.41)

Key: CI=Confidence Interval; EOI=Event(s) of Interest; EU=European Union; LB=Lower Bound; O/E=Observed versus Expected; PE=Point Estimate; RP=Reporting Percentage; US=United States

a: Counts included EOI (from valid cases) with that occurred within the risk window (Day: 1 to 30) only.

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

The US restricted sensitivity analysis showed an O/E ratio of >1 for both age groups. The O/E ratio was statistically significant above 1 (lower bound of 95% confidence interval >1) for both age groups. The EU restricted sensitivity analysis showed a statistically significant O/E ratio of>1 (lower bound of 95% confidence interval <1) for the 18 to 59 age group. Since the previous PBRER DLP (24 February 2022), for the EU 18 to 59 and ≥60 age groups, the restricted sensitivity O/E ratio showed an increase from <1 to >1. The O/E ratio was statistically significant above 1 (lower bound of 95% confidence interval >1) in the EU for the 18 to 59 age group.

MAH conclusion

Based on the evaluation of the cases, and review of safety from other sources, the information is consistent with the information known about cardiomyopathy. The Company will continue to closely monitor cardiomyopathy as an AESI.

Rapporteur assessment comment:

During the interval reporting period of 25 February 2022 to 24 August 2022, 17 (12 medically confirmed and 5 medically unconfirmed) initial, primary dose cases reporting cardiomyopathy were identified. Cumulatively, 74 (49 medically confirmed and 25 medically unconfirmed) primary dose cases reporting cardiomyopathy were identified. During the interval reporting period, 1 initial case reported as booster was identified (medically unconfirmed; 4 cases cumulatively). As seen already in earlier PSURs and MSSRs (detailed investigation of this term performed in MSSR6) O/E ratios are significantly increased with emphasis on the US data. No additional new concern is raised with the presentation of the current interval data.

Coronary Artery Disease, Including Acute Myocardial Infarction

Coronary artery disease (CAD), including acute myocardial infarction (AMI) is listed as an AESI in the cRMP, EU RMP, and the US PVP.

Primary Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 204 (114 medically confirmed and 90 medically unconfirmed) initial, primary dose cases reporting CAD, including acute MI were identified. Of these 204 cases, 203 were serious and 1 was nonserious and reported a total of 230 EOI (228 serious; 2 nonserious). Of these 204 primary dose cases received during the interval reporting period, 62 were reported from Janssen Sponsored Clinical Studies and 142 from post-marketing sources (including spontaneous and solicited cases). No cases were reported from Janssen Supported Clinical Studies. Cumulatively, 920 (544 medically confirmed and 376 medically unconfirmed) primary dose cases

reporting CAD, including acute MI were identified. Of these cases, 914 were serious and 6 were nonserious and reported a total of 1,105 EOI (1,092 serious; 13 nonserious). Of the 920 cumulative primary dose cases received, 192 were reported from Janssen Sponsored Clinical Studies, 3 from Janssen Supported Clinical Studies, and 725 from post-marketing sources (including spontaneous and solicited cases).

Janssen Sponsored Clinical Studies Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 62 initial, primary dose cases reporting CAD, including acute MI were retrieved from Janssen Sponsored Clinical Studies. Of the 62 cases, 32 were from VAC31518COV3001 and 30 from VAC31518COV3009. These 62 cases reported 62 serious EOI. Of these 62 cases, the most frequently reported countries/territories of origin (n≥10) were the US (n=22), followed by Brazil (n=10). These cases concerned 44 males and 18 females. The age range was from 33 to 90 years. The EOI (n≥5) included acute myocardial infarction (n=14), coronary artery disease and myocardial infarction (n=11 each), and arteriosclerosis coronary artery (n=5). The mean and median TTO were 353.9 and 350.5 days, respectively. The outcomes were resolved (n=37), fatal and resolving (n=7 each), not resolved (n=6), and resolved with sequelae (n=5).

Post-marketing Sources (Including Spontaneous and Solicited) Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 142 post-marketing sources (including spontaneous and solicited), initial, primary dose cases reporting CAD, including acute MI were retrieved. These 142 initial, post-marketing, primary dose cases reported 168 EOI (166 serious; 2 nonserious). Cumulatively, 725 (349 medically confirmed and 376 medically unconfirmed) post-marketing, primary dose cases reporting CAD, including acute MI were identified. Of these cases, 721 were serious and 4 were nonserious and reported a total of 903 EOI (892 serious; 11 nonserious). Of these 142 post-marketing, initial, primary dose cases, the most frequently reported countries/territories of origin (n≥43) were the US (n=44), followed by Germany (n=43). These cases concerned 95 males, 44 females, and 3 did not report sex. The age range was from 19 to 96 years. The frequency distribution of the MedDRA PTs of interest reported in post-marketing, primary dose cases is presented in Table 118 below. A single case may contain more than 1 EOI.

The EOI (n>20) included angina pectoris (n=63), myocardial infarction (n=38), and acute myocardial infarction (n=21). The mean and median TTO were 81.6 and 14.0 days, respectively. Where reported (n=131), the outcomes were not resolved (n=46), resolved (n=30), fatal (n=24), resolving (n=21), and resolved with sequelae (n=10).

Table 118: Frequency of MedDRA PTs of Interest in Post-Marketing, Primary Dose Cases Reporting Coronary Artery Disease, Including Acute Myocardial Infarction With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Angina pectoris	63	0	185	0
Myocardial infarction	38	0	272	0
Acute myocardial infarction	21	0	137	0

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

a: The MedDRA PTs of interest with a frequency ≥20 have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event of interest.

Fatal Post-marketing Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 18 post-marketing, initial, primary dose fatal cases with 26 fatal EOI were retrieved. The fatal EOI were myocardial infarction (n=12), acute

myocardial infarction (n=6), troponin increased, coronary artery thrombosis (n=2 each), and arteriosclerosis coronary artery, coronary arterial stent insertion, myocardial ischaemia, and percutaneous coronary intervention (n=1 each). Four fatal cases reported a TTO within the risk window of 28 days. All 4 cases are medically confirmed. Patient age ranged from 38 to 96 years, and TTO was reported in 3 cases and ranged from 4 to 16 days post-vaccination. The cause of death was reported due to MI (n=2), MI and coronary artery thrombosis (n=1), acute kidney injury, acute MI, anaemia of chronic disease, aspiration, atrial fibrillation, azotaemia, condition aggravated, confusional state, delirium, disease progression, encephalopathy, end-stage renal disease, general physical health deterioration, hyperkalaemia, hypernatraemia, metabolic acidosis, metabolic encephalopathy, multimorbidity, myocardial ischaemia, pneumonia aspiration, rhabdomyolysis, superficial vein thrombosis, and troponin increased (n=1). Of these 4 cases, 3 contained evidence of an alternative aetiology/identified risk factor for the development of an EOI. This included concurrent conditions of coronary sclerosis (n=1), hypertension (n=1), and chronic kidney disease (n=1). The remaining case was reported in a 38-year-old female who experienced an MI on an unspecified date post-vaccination. This case lacked essential information (medical history/concurrent conditions, latency, autopsy report, clinical course details including diagnostic/laboratory workup, and concomitant medications) precluding any meaningful medical assessment. Fourteen cases reported TTO outside of the risk window of 28 days. Twelve cases were medically confirmed, and 2 were medically unconfirmed. Patient age ranged from 29 to 94 years and the TTO ranged from 35 to 310 days post-vaccination. The cause of death was reported due to MI (n=7), unspecified cause (n=4), AMI, Sepsis and COVID-19 pneumonia (n=1), MI, hypertension, and hypertensive heart disease (n=1), and MI and COVID-19 infection (n=1). The majority of the cases (13/14, 93%) reported an alternative aetiology/identified risk factor for the development of an EOI. This included underlying cardiac history (n=6), concurrent COVID-19 infection (n=5), sepsis (n=1), and obstructive sleep apnoea, and hyperlipidaemia (n=1). The remaining case lacked essential information (medical history/concurrent conditions, autopsy report, clinical course details including diagnostic/laboratory workup, and concomitant medications) precluding any meaningful medical assessment. Of these 14 cases, 1 reported the age of the patient as < 40 years. A summary of the case is shown below: A 29-year-old male who was reported as healthy with no current illnesses or known allergies, experienced sepsis, MI, and organ failure 131 days post-vaccination. Five days later, the patient died from an unknown cause. It was not reported whether an autopsy was performed.

Booster Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 27 (7 medically confirmed and 20 medically unconfirmed) initial cases reported as booster were identified. All 27 cases were serious and reported a total of 29 serious EOI. Of these cases, 16 were heterologous and 11 were homologous. Of these 27 cases reported as booster during the interval, 1 was reported from a Janssen Sponsored Clinical Study and 26 from post-marketing spontaneous sources. No cases were reported from Janssen Supported Clinical Studies. Cumulatively, 44 (15 medically confirmed and 29 medically unconfirmed) cases reported as booster were identified. All 44 cases were serious and reported a total of 50 serious EOI. Of these cases, 25 were heterologous and 19 were homologous. Of the 44 cumulative booster dose cases received, 1 was reported from a Janssen Sponsored Clinical Study, 1 from a Janssen Supported Clinical Study, and 42 from post-marketing spontaneous sources.

Janssen Sponsored Clinical Studies Booster Dose Cases

During the interval reporting period of 25 February 2022 to 24 August 2022, 1 initial case reported as booster was retrieved from a Janssen Sponsored Clinical Study. This case was reported from VAC31518COV3001 and concerned a 56-year-old male from [redacted] who experienced a serious EOI of

acute coronary syndrome. The TTO was reported as 120 days from the first dose and the outcome was reported as resolving.

Post-marketing Sources (Including Spontaneous and Solicited) Booster Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 26 post-marketing sources (including spontaneous and solicited), initial cases reported as booster were retrieved. These 26 post-marketing, booster dose cases reported 28 serious EOI. Cumulatively, 42 (13 medically confirmed and 29 medically unconfirmed) post-marketing cases reported as booster were identified. All 42 cases were serious and reported a total of 48 serious EOI. Of these 26 post-marketing, initial cases reported as booster, the most frequently reported countries/territories of origin (n≥2) were Austria, Germany, and the US (n=7 each), followed by Brazil (n=2). These cases concerned 17 males and 9 females. The age range was from 13 to 84 years. The frequency distribution of the MedDRA PTs of interest reported in post-marketing cases reported as booster is presented in Table 120 below. A single case may contain more than 1 EOI.

The EOI (n≥6) included angina pectoris (n=14) and myocardial infarction (n=6). The mean and median TTO were 90.8 and 42.5 days, respectively. Where reported (n=24), the outcomes were not resolved (n=9), resolved (n=8), fatal (n=4), and resolving (n=3).

Table 120: Frequency of MedDRA PTs of Interest in Post-marketing Cases Reported as Booster Dose With the Use of Ad26.COV2.S and Reporting Coronary Artery Disease, Including Acute Myocardial Infarction

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Angina pectoris	14	0	16	0
Myocardial infarction	6	0	15	0

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

a: The MedDRA PTs of interest with a frequency ≥6 have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event of interest.

Fatal Post-marketing Booster Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 5 initial, fatal cases reported as booster with 5 fatal EOI were retrieved. The fatal EOI were myocardial infarction (n=4) and acute myocardial infarction (n=1).

Homologous Booster Dose

One case reported a fatal EOI following a booster with Ad26.COV2.S. This case is medically unconfirmed and concerned a 55-year-old male who received 3 doses of Ad26.COV2.S. It was unknown whether the patient had experienced AEs following vaccination with the first 2 doses of Ad26.COV2.S. Two weeks after the third dose, the patient experienced what was described as a massive heart attack. On an unspecified date post-vaccination, the patient died from an unknown cause. It was unknown if an autopsy was performed. This case lacked essential information (medical history/concurrent conditions, clinical course details including diagnostic/laboratory workup, concomitant medications, and autopsy results) precluding any meaningful medical assessment.

Heterologous Booster Dose

Four cases involved a heterologous booster, where Ad26.COV2.S vaccine was reported as the primary dose and the booster dose was an mRNA vaccine. The EOI was reported in relation to the mRNA booster. The cause of death in these 4 cases was MI and thrombosis (n=2), MI (n=1), and AMI (n=1).

Literature ICSR

No information was identified that would change the characterisation of risk.

O/E Analysis Results

Since the previous PBRER data lock point (24 February 2022), the broad O/E ratio has remained <1 in the US and EU for both age groups. A restricted O/E analysis with sensitivity analysis was not required.

MAH Conclusion

Based on the evaluation of the cases, and review of safety from other sources, the information is consistent with the information known about coronary artery disease, including acute myocardial infarction. The Company will continue to closely monitor coronary artery disease, including acute myocardial infarction as an AESI.

Rapporteur assessment comment:
No new safety concern is detected with CAD and MI.

Musculoskeletal Disorders

Acute Aseptic Arthritis

Acute aseptic arthritis is listed as an AESI in the cRMP, EU RMP, and the US PVP.

Primary Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 143 (66 medically confirmed and 77 medically unconfirmed) initial, primary dose cases reporting acute aseptic arthritis were identified. Of these 143 cases, 110 were serious and 33 were nonserious and reported a total of 153 EOI (109 serious; 44 nonserious). Of these 143 primary dose cases received during the interval reporting period, 41 were reported from Janssen Sponsored Clinical Studies and 102 from post-marketing sources (including spontaneous and solicited cases). No cases were reported from Janssen Supported Clinical Studies. Cumulatively, 610 (356 medically confirmed and 254 medically unconfirmed) primary dose cases reporting acute aseptic arthritis were identified. Of these cases, 349 were serious and 261 were nonserious and reported a total of 637 EOI (328 serious; 309 nonserious). Of the 610 cumulative primary dose cases received, 100 were reported from Janssen Sponsored Clinical Studies, 2 from Janssen Supported Clinical Studies, and 508 from post-marketing sources (including spontaneous and solicited cases).

Janssen Sponsored Clinical Studies Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 41 initial, primary dose cases reporting acute aseptic arthritis were retrieved from Janssen Sponsored Clinical Studies. Of the 41 cases, 22 were from VAC31518COV3009, 17 from VAC31518COV3001, and 1 each from VAC31518COV2008 and VAC31518COV3005. These 41 cases reported 43 EOI (42 serious; 1 nonserious). Of these 41 cases, the most frequently reported countries/territories of origin (n≥12) were the US (n=17), followed by Belgium (n=12). These cases concerned 22 females and 19 males. The age range was from 20 to 82 years. The EOI (≥2) included osteoarthritis (n=35) and spinal osteoarthritis and temporomandibular joint syndrome (n=2 each). The mean and median TTO were 333.4 and 353.0 days, respectively. Where reported

(n=42), the outcomes were resolved (n=29), resolving (n=6), resolved with sequelae (n=4), not resolved (n=2), and fatal (n=1).

Post-marketing Sources (Including Spontaneous and Solicited) Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 102 post-marketing sources (including spontaneous and solicited), initial, primary dose cases reporting acute aseptic arthritis were retrieved. These 102 post-marketing, initial, primary dose cases reported 110 EOI (67 serious; 43 nonserious). Cumulatively, 508 (254 medically confirmed and 254 medically unconfirmed) post-marketing, primary dose cases reporting acute aseptic arthritis were identified. Of these cases, 249 cases were serious and 259 were nonserious and reported a total of 533 EOI (227 serious; 306 nonserious). Of these 102 post-marketing, initial, primary dose cases, the most frequently reported countries/territories of origin (n≥32) were the US (n=39), followed by Germany (n=32). These cases concerned 62 females, 37 males, and 3 did not report sex. The age range was from 14 to 77 years.

The EOI (≥5) included arthritis and rheumatoid arthritis (n=28 each), periarthritis (n=11), rheumatic disorder (n=8), osteoarthritis (n=6), and polyarthritis (n=5). The mean and median TTO were 28.8 and 8.0 days, respectively. Where reported (n=95), the outcomes were not resolved (n=65), resolved and resolving (n=11 each), resolved with sequelae (n=6), and fatal (n=2).

Table 122: Frequency of MedDRA PTs of Interest in Post-marketing, Primary Dose Cases Reporting Acute Aseptic Arthritis With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Arthritis	9	19	33	225
Rheumatoid arthritis	28	0	92	0
Periarthritis	4	7	14	17
Rheumatic disorder	1	7	2	16
Osteoarthritis	2	4	9	14
Polyarthritis	5	0	17	0

Table 122: Frequency of MedDRA PTs of Interest in Post-marketing, Primary Dose Cases Reporting Acute Aseptic Arthritis With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious

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

a: The MedDRA PTs of interest with a frequency ≥5 have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event of interest.

From the 102 post-marketing, initial, primary dose cases, 2 concerned a 59-year-old male and a 46-year-old female, who experienced rheumatoid arthritis 1 and 13 days post-vaccination with Ad26.COV2.S respectively. There were no identified risk factors/confounders that could have led to the EOI. Considering the plausible temporal relation and an absence of alternate aetiologies, causality with the vaccine cannot be excluded in these 2 cases.

Fatal Post-marketing Primary Dose Cases

During the reporting period, 2 post-marketing, primary dose fatal cases with 2 fatal EOI were retrieved. The fatal EOI were gout and gouty tophus. The first case concerned a 48-year-old male, where the fatal event of gout occurred 303 days post-vaccination. The case provided limited information on clinical course, diagnostic workup, date ofdeath, and autopsy details which precludes a meaningful medical assessment. The second case reporting fatal gouty tophus 26 days post-vaccination concerned a 46-year-

old male with concurrent events of colorectal cancer, ileus secondary to ileocecal tuberculosis and hospital acquired pneumonia with subsequent septic shock, which could provide an alternate explanation to the fatal outcome. It was unknown if autopsy was performed in either case.

Booster Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 28 (6 medically confirmed and 22 medically unconfirmed) initial cases reported as booster were identified. There were 16 serious and 12 nonserious cases and reported a total of 31 EOI (13 serious; 18 nonserious). Of these cases, 19 were heterologous and 9 were homologous. Of these 28 cases reported as booster during the interval, all were reported from post-marketing sources (including spontaneous and solicited). No cases were reported from Janssen Sponsored Clinical Studies or Janssen Supported Clinical Studies. Cumulatively, 35 (8 medically confirmed and 27 medically unconfirmed) cases reported as booster were identified. Of these cases, 19 were serious and 16 were nonserious and reported a total of 38 EOI (16 serious; 22 nonserious). Of these cases, 19 were heterologous and 16 were homologous. Of the 35 cumulative booster dose cases received, all were reported from post-marketing sources (including spontaneous and solicited). No cases were reported from Janssen Sponsored Clinical Studies or Janssen Supported Clinical Studies.

Post-marketing Sources (Including Spontaneous and Solicited) Booster Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 28 post-marketing sources (including spontaneous and solicited), initial cases reported as booster were retrieved. These 28 post-marketing, initial, booster dose cases reported 31 EOI (13 serious; 18 nonserious). Cumulatively, 35 (8 medically confirmed and 27 medically unconfirmed) post-marketing cases reported as booster were identified. Of these cases, 19 were serious and 16 were nonserious and reported a total of 38 EOI (16 serious; 22 nonserious). Of these 24 post-marketing, initial cases reported as booster, the most frequently reported countries/territories of origin (n≥9) were Germany (n=10), followed by the US (n=9). These cases concerned 15 males, 12 females, and 1 did not report sex. The age range was from 34 to 80 years. The EOI (≥2) included arthritis (n=14), rheumatoid arthritis (n=6), osteoarthritis (n=3), and gout and rheumatic disorder (n=2 each). The mean and median TTO were 127.5 and 166.0 days, respectively. Where reported (n=24), the outcomes were not resolved (n=16), resolved with sequelae (n=3), resolved and resolving (n=2 each), and fatal (n=1).

Table 124: Frequency of MedDRA PTs of Interest in Post-marketing Cases Reported as Booster Dose With the Use of Ad26.COV2.S and Reporting Acute Aseptic Arthritis

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Arthritis	2	12	2	16
Rheumatoid arthritis	6	0	8	0
Osteoarthritis	2	1	2	1
Gout	1	1	1	1
Rheumatic disorder	0	2	0	2

Fatal Post-marketing Booster Dose Cases

During the reporting period, 1 fatal case reported as booster with 1 fatal EOI was retrieved. The fatal EOI was arthritis. The case concerned a 74-year-old male with a medical history significant for a mild stroke and concurrent hypertension, who experienced the EOI 301 days post primary dose with Ad26.COV2.S, 155 days post booster dose with elasomeran (Dose 2) and 1 day post booster dose with tozinameran

(Dose 3). The case was missing information on clinical course leading up the patient's death, diagnostic workup, and autopsy details, which precludes a meaningful medical assessment. It was unknown if autopsy was performed.

Table 124: Frequency of MedDRA PTs of Interest in Post-marketing Cases Reported as Booster Dose With the Use of Ad26.COV2.S and Reporting Acute Aseptic Arthritis

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: The MedDRA PTs of interest with a frequency ≥2 have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022).

Literature ICSR

No ICSR literature cases were received during the reporting period of 25 February 2022 to 24 August 2022.

O/E Analysis Results

Since the previous PBRER DLP (24 February 2022), the broad O/E ratio has remained <1 in the US and EU for both age groups. A restricted O/E analysis with sensitivity analysis was not required.

MAH Conclusion

Based on the evaluation of the cases, and review of safety from other sources, the information is consistent with the information known about acute aseptic arthritis. The Company will continue to closely monitor acute aseptic arthritis as an AESI.

Rapporteur assessment comment:

O/E ratios are clearly <1 for the US and the EU. No new safety concern is detected with arthritis.

Nervous System Disorders

Generalized Convulsion

Generalized convulsion is listed as an AESI in the cRMP, EU RMP, and the US PVP.

Primary Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 168 (106 medically confirmed and 62 medically unconfirmed) initial, primary dose cases reporting generalised convulsion were identified. Of these 168 cases, 153 were serious and 15 were nonserious and reported a total of 169 EOI (154 serious; 15 nonserious). Of these 168 initial, primary dose cases received during the interval reporting period, 10 were reported from Janssen Sponsored Clinical Studies and 158 from post-marketing sources (including spontaneous and solicited cases). No cases were reported from Janssen Supported Clinical Studies. Cumulatively, 559 (303 medically confirmed and 256 medically unconfirmed) primary dose cases reporting generalised convulsion were identified. Of these cases, 537 cases were serious and 22 were nonserious and reported a total of 578 EOI (551 serious; 27 nonserious). Of the 559 cumulative primary dose cases received, 17 were reported from Janssen Sponsored Clinical Studies, 7 from Janssen

Supported Clinical Studies, and 535 from post-marketing sources (including spontaneous and solicited cases).

Janssen Sponsored Clinical Studies PrimaryDose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 10 initial, primary dose cases reporting generalised convulsion were retrieved from Janssen Sponsored Clinical Studies. Of the 10 cases, 6 were from VAC31518COV3001 and 2 each from VAC31518COV3009 and VAC31518COV2008. These 10 cases reported 10 serious EOI. Of these 10 cases, the most frequently reported countries/territories of origin were South Africa (n=5), followed by the US (n=4). These cases concerned 6 females and 4 males. The age range was from 35 to 80 years. The EOI included seizure (n=6) and epilepsy, generalised tonic-clonic seizure, hyperglycaemic seizure, and partial seizures (n=1 each). The mean and median TTO were 351.8 and 403.0 days, respectively. The outcomes were reported as resolved (n=6) and fatal, not resolved, resolved with sequelae, and resolving (n=1 each).

Post-marketing Sources (Including Spontaneous and Solicited) Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 158 post-marketing sources (including spontaneous and solicited), initial, primary dose cases reporting generalized convulsion were retrieved. These 158 post-marketing, initial, primary dose cases reported 159 EOI (144 serious; 15 nonserious).

Cumulatively, 535 (279 medically confirmed and 256 medically unconfirmed) post-marketing, primary dose cases reporting generalised convulsion were identified. Of these cases, 514 were serious and 21 were nonserious and reported a total of 554 EOI (528 serious; 26 nonserious). Of these 158 post-marketing, initial, primary dose cases, the most frequently reported countries/territories of origin (n≥11) were Poland (n=99), followed by South Africa (n=15), and Germany (n=11). These cases concerned 52 males, 45 females, and 61 did not report sex. The age range was from 16 to 79 years. The EOI (≥4) included seizure (n=122), febrile convulsion (n=21), epilepsy (n=8), and generalized tonic-clonic seizure (n=4). The mean and median TTO were 10.9 and 0 days, respectively. Where reported (n=100), the outcomes were resolved (n=43), resolving (n=34), not resolved (n=18), resolved with sequelae (n=4), and fatal (n=1).

Table 126: Frequency of MedDRA PTs of Interest in Post-marketing, Primary Dose Cases Reporting Generalised Convulsion With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Seizure	122	0	391	0
Febrile convulsion	6	15	11	20
Epilepsy	8	0	42	0
Generalised tonic-clonic seizure	4	0	38	0

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

a: The MedDRA PTs of interest with a frequency ≥4 have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event of interest.

Fatal Post-marketing Primary Dose Cases

During the reporting period, 2 post-marketing, initial, primary dose fatal cases, each reporting 1 fatal EOI, were retrieved. The fatal EOI were epilepsy in 1 case and seizure in the other. Both cases were medically confirmed. One case was reported from a clinical trial (VAC3118COV3009) and concerned a 37-year-old female with a medical history of epilepsy and morbid obesity (Body Mass Index 41.6). Concomitant medications included ethinylestradiol/levonorgestrel for contraception. On Day 426 after

primary vaccination with Ad26.COV2.S and Day 376 after booster dose of Ad26.COV2.S, the patient experienced epilepsy and died. No autopsy was performed and the death certificate was not provided. The Investigator's causality assessment for the EOI and Ad26.COV2.S was reported as not related. TTO of the EOI was well beyond the risk window for convulsions/seizures. History of loss of consciousness at the time of the EOI, and tonic, clonic, tonic-clonic or atonic motor manifestations were not reported. This case lacked essential details (treatment of the patient's underlying epilepsy, clinical course and treatment of the EOI, or laboratory results and diagnostic testing), which precluded a meaningful medical assessment. Additionally, the patient's underlying epilepsy provide an alternative aetiology for the EOI, and obesity and hormonal contraception may have been contributory factors. The other case concerned a 24-year-old male who experienced generalised weakness, loss of consciousness, and seizure on Day 1 after vaccination and died 2 days later. Although loss of consciousness at the time of the EOI was reported, it was not reported if the patient had a history of loss of consciousness or experienced tonic, clonic, tonic-clonic or atonic motor manifestations at the time of the EOI. Essential details (medical history/concurrent conditions, concomitant medications, clinical course for EOI, treatment, laboratory results, diagnostic testing) were not reported, which precluded a meaningful medical assessment. It was not known if an autopsy was performed.

Booster Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 11 (2 medically confirmed and 9 medically unconfirmed) initial cases reported as booster were identified. All 11 cases were serious and reported a total of 12 serious EOI. Of these cases, 6 were homologous and 5 were heterologous. Of these 11 cases reported as booster during the interval, all were from post-marketing sources (including spontaneous and solicited). No cases were reported from Janssen Sponsored Clinical Studies or Janssen Supported Clinical Studies. Cumulatively, 16 (7 medically confirmed and 9 medically unconfirmed) cases reported as booster were identified. All 16 cases were serious and reported a total of 17 serious EOI. Of these cases, 9 were homologous and 7 were heterologous. Of the 16 cumulative booster dose cases received, 1 was reported from a Janssen Supported Clinical Study and 15 from post-marketing sources (including spontaneous and solicited cases). No cases were reported from Janssen Sponsored Clinical Studies.

Post-marketing Sources (Including Spontaneous and Solicited) Booster Dose Cases

During the reporting period, 11 post-marketing sources (including spontaneous and solicited), initial cases reported as booster were retrieved. These 11 post-marketing, initial booster dose cases reported 12 serious EOI.

Cumulatively 15 (6 medically confirmed and 9 medically unconfirmed) post-marketing cases reported as booster were identified. All 15 cases were serious and reported a total of 16 serious EOI. Of these 11 post-marketing, initial cases reported as booster, the most frequently reported countries/territories of origin (n≥3) were Germany (n=4), followed by Brazil and the US (n=3 each). These cases concerned 7 females, 3 males, and 1 did not report sex. The age range was from 20 to 56 years. The EOI included seizure (n=8), epilepsy (n=3), and generalised tonic-clonic seizure (n=1). The mean and median TTO were 61.1 and 9.0 days, respectively. Where reported (n=8), the outcomes were not resolved and resolved (n=3 each) and resolving (n=2).

Table 128: Frequency of MedDRA PTs of Interest in Post-marketing Cases Reported as Booster Dose With the Use of Ad26.COV2.S and Reporting Generalised Convulsion

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Seizure	8	0	11	0
Epilepsy	3	0	4	0
Generalised tonic-clonic seizure	1	0	1	0

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: The MedDRA PTs of interest have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event of interest.

There were no fatal cases reported as booster which were retrieved from the search of the Company global safety database during the interval reporting period.

Literature ICSR

No ICSR literature cases were received during the reporting period of 25 February 2022 to 24 August 2022.

O/E Analysis Results

Table 129: Generalised Convulsions: Restricted O/E and Sensitivity Analysis Results – (Cumulative Through 24 August 2022)

Restricted 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	43.76	0.17	(0.12, 0.23)	0.38	(0.28, 0.52)

Key: CI=Confidence Interval; EOI=Event(s) of Interest; EU=European Union; LB=Lower Bound; O/E=Observed versus Expected; PE=Point Estimate; RP=Reporting Percentage; US=United States
a: Counts included EOI (from valid cases) that occurred within the risk window (Day: 1 to 14) only.
b: Poisson exact confidence interval (95% CI).

The EU restricted sensitivity analysis showed an O/E ratio of<1 for the 18 to 59 age group.

MAH Conclusion

Based on the evaluation of the cases, and review of safety from other sources, the information is consistent with the information known about generalised convulsion. The Company will continue to closely monitor generalised convulsion as an AESI.

Rapporteur assessment comment:

During the interval reporting period of 25 February 2022 to 24 August 2022, 168 (106 medically confirmed and 62 medically unconfirmed) initial, primary dose cases reporting generalised convulsion were identified. Of these, 153 were serious. A majority (n=158) were from post-marketing sources, most of them from Poland (n=99), and the most commonly reported PT was seizure (n=122). In addition, 12 cases were reported as booster doses. The O/E ratio was <1.

No new safety concern was detected here.

Encephalitis, Including Acute Disseminated Encephalomyelitis and Meningoencephalitis

Encephalitis, including acute disseminated encephalomyelitis and meningoencephalitis (ADEM) is listed as an AESI in the cRMP, EU RMP, and the US PVP.

Primary Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 11 (8 medically confirmed and 3 medically unconfirmed) initial, primary dose cases reporting encephalitis, including ADEM and meningoencephalitis were identified. All 11 cases were serious and reported a total of 12 serious EOI. All 11 primary dose cases received during the interval were reported from post-marketing sources (including spontaneous and solicited). No cases were reported from Janssen Sponsored Clinical Studies or Janssen Supported Clinical Studies. Cumulatively, 88 (62 medically confirmed and 26 medically unconfirmed) primary dose cases reporting encephalitis, including ADEM and meningoencephalitis were identified. All 88 cases were serious and reported a total of 92 serious EOI. Of the 88 cumulative primary dose cases received, 2 were reported from Janssen Sponsored Clinical Studies, 3 from Janssen Supported Clinical Studies, and 83 from post-marketing sources (including spontaneous and solicited cases).

Post-marketing Sources (Including Spontaneous and Solicited) Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 11 post-marketing sources (including spontaneous and solicited), initial, primary dose cases reporting encephalitis, including ADEM and meningoencephalitis were retrieved. These 11 post-marketing, initial, primary dose cases reported 12 serious EOI. Cumulatively, 83 (57 medically confirmed and 26 medically unconfirmed) post-marketing, primary dose cases reporting encephalitis, including ADEM and meningoencephalitis were identified. All 83 cases were serious and reported a total of 87 serious EOI. Of these 11 post-marketing, initial, primary dose cases, the most frequently reported countries/territories of origin (n≥2) were Germany (n=3), followed by the US (n=2). These cases concerned 5 females, 4 males, and 2 did not report sex. The age range was from 17 to 65 years.

The EOI (≥2) included acute disseminated encephalomyelitis (n=4) and encephalitis, encephalomyelitis, and noninfective encephalitis (n=2 each). The mean and median TTO were 22.5 and 12.0 days respectively. Where reported (n=8), the outcomes were not resolved (n=3), resolving (n=2), and fatal, resolved, and resolved with sequelae (n=1 each).

Table 131: Frequency of MedDRA PTs of Interest in Post-marketing, Primary Dose Cases Reporting Encephalitis, Including ADEM and Meningoencephalitis With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Acute disseminated encephalomyelitis	4	0	18	0
Encephalitis	2	0	40	0
Encephalomyelitis	2	0	9	0
Noninfective encephalitis	2	0	12	0
Encephalitis haemorrhagic	1	0	1	0
Limbic encephalitis	1	0	2	0

Key: ADEM=Acute Disseminated Encephalomyelitis; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term

a: The MedDRA PTs of interest have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event of interest.

Fatal Post-marketing Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 1 post-marketing, initial, primary dose fatal case with 1 fatal EOI was retrieved. This literature case report concerned a 45-year-old male with a history of diabetes mellitus who experienced haemorrhagic encephalitis along with Tolosa-Hunt syndrome and infectious/autoimmune vasculitis on an unspecified day post-vaccination. The patient was reported as positive for SARS-CoV-2 by transcription-polymerase chain reaction. Considering the lack of information on temporal relationship for the EOI and the patient's serious underlying conditions, including COVID-19 infection, causal association with vaccination is unlikely.

Booster Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 2 (no medically confirmed and 2 medically unconfirmed) initial cases reported as booster were identified. Both cases were serious and reported a total of 2 serious EOI. Of these cases, 1 was heterologous and 1 was homologous. Both cases reported as booster during the interval were from post-marketing sources (including spontaneous and solicited). No cases were reported from Janssen Sponsored Clinical Studies or Janssen Supported Clinical Studies. Cumulatively, the afore mentioned 2 medically unconfirmed cases reported as booster were identified.

Post-marketing Sources (Including Spontaneous and Solicited) Booster Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 2 post-marketing sources (including spontaneous and solicited), initial cases reported as booster were retrieved. These 2 post-marketing, initial, booster dose cases reported 2 serious EOI. Of these 2 post-marketing, booster dose cases, 1 case concerned a 76-year-old female from [redacted] and the second case concerned a 52-year-old male from [redacted]. The EOI included acute disseminated encephalomyelitis and encephalitis. The mean and median TTO was 7.5 days. Where reported (n=1), the outcome was not resolved. Cumulatively, the aforementioned 2 medically unconfirmed post-marketing cases reported as booster were identified.

There were no initial, fatal cases reported as booster which were retrieved from the search of the Company global safety database during the interval reporting period.

Literature ICSR

No information was identified that would change the characterisation of risk.

O/E Analysis Results

PRAC endorsed (Procedure Number: EMEA/H/C/PSUSA/00010916/202202) the removal of"*SMQ ""Noninfectious Encephalopathy/Delirium" and "Noninfectious meningitis*" for the MedDRA O/E search strategy. The O/E MedDRA search strategy for Encephalitis was updated to Noninfectious Encephalitis SMQ (Narrow) only

Table 132: Encephalitis, ADEM Alone: Restricted O/E and Sensitivity Analysis Results (Cumulative Through 24 August 2022)

Restricted O/E Analysis						Sensitivity Analysis	
AESI	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)	
Encephalitis	US	18 to 59	13.30	0.11	(0.06, 0.18)	1.84	(0.99, 3.13)
		≥60	3.68	0.04	(0.01, 0.11)	0.65	(0.16, 1.73)
	EU	18 to 59	20.00	0.14	(0.09, 0.22)	2.42	(1.48, 3.74)
ADEM	US	18 to 59	7.65	0.61	(0.26, 1.22)	3.18	(1.34, 6.36)
	EU	18 to 59	4.00	0.28	(0.08, 0.72)	1.45	(0.40, 3.72)

Key: ADEM=Acute disseminated encephalomyelitis; CI=Confidence Interval; EU=European Union; EOI=Event(s) of Interest; LB=Lower Bound; O/E=Observed versus Expected; PE=Point Estimate; RP=Reporting Percentage; US=United States

a: Counts included EOI (from valid cases) that occurred within the risk window (Day: 1 to 42) only.

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

Encephalitis

The US restricted sensitivity analysis showed an O/E ratio of >1 for the 18 to 59 age group only. This O/E ratio was not statistically significant above 1 (lower bound of 95% confidence interval <1). The EU restricted sensitivity analysis showed an O/E ratio of >1 in the 18 to 59 age group. This O/E ratio was statistically significant above 1 (lower bound of 95% confidence interval >1). Since the previous PBRER DLP (24 February2022), the US ≥60 age group restricted sensitivity O/E ratio changed from >1 to <1. This was attributed to the change in the MedDRA search strategy for Encephalitis.

ADEM

The US restricted sensitivity analysis showed an O/E ratio of >1 for the 18 to 59 age group. This O/E ratio was statistically significant above 1 (lower bound of 95% confidence interval >1). The EU restricted sensitivity analysis showed an O/E ratio of >1 for the 18 to 59 age group. This O/E ratio was not statistically significant above 1 (lower bound of 95% confidence interval <1). Since the previous PBRER DLP (24 February 2022), for the EU 18 to 59 age group, the restricted sensitivity O/E ratio showed an increase from <1 to >1. The O/E ratio was not statistically significant above 1 (lower bound of 95% confidence interval >1).

Conclusion

Based on the evaluation of the cases, and review of safety from other sources, the information is consistent with the information known about encephalitis, including ADEM and meningoencephalitis. The Company will continue to closely monitor cases of encephalitis, including ADEM and meningoencephalitis, as an AESI.

Rapporteur assessment comment: This AESI has been evaluated in depth in earlier SSRs and no new safety information has been identified in these reports. No additional safety concern is detected in this PSUR. The MAH will continue to closely monitor cases of encephalitis, including ADEM and meningoencephalitis, as an AESI, which is endorsed.

Multiple Sclerosis (Including Optic Neuritis)

Multiple sclerosis, including optic neuritis is listed as an AESI in the cRMP, EU RMP, and the US PVP.

Primary Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 14 (8 medically confirmed and 6 medically unconfirmed) initial, primary dose cases reporting multiple sclerosis, including optic neuritis were identified. All 14 cases were serious and reported a total of 14 serious EOI. Of these 14 initial, primary dose cases received during the interval reporting period, 2 were reported from Janssen Sponsored Clinical Studies and 12 from post-marketing sources (including spontaneous and solicited). No cases were reported from Janssen Supported Clinical Studies. Cumulatively, 71 (37 medically confirmed and 34 medically unconfirmed) primary dose cases reporting multiple sclerosis, including optic neuritis were identified. All 71 cases were serious and reported a total of 73 serious EOI. Of the 71 cumulative primary dose cases received, 3 were reported from Janssen Sponsored Clinical Studies, 1 from a Janssen Supported Clinical Study, and 67 from post-marketing sources (including spontaneous and solicited cases).

Janssen Sponsored Clinical Studies Primary Dose Cases

During the reporting period, 2 initial, primary dose cases reporting multiple sclerosis, including optic neuritis were retrieved from Janssen Sponsored Clinical Studies. Both cases were from VAC31518COV3001. These 2 cases reported 2 serious EOI. The reported country/territory of origin was [redacted]. Both cases concerned females. The age was reported as 47 and 66 years. The EOI included multiple sclerosis (n=2). The mean and median TTO were 388.5 days each. The outcomes for the reported EOI were resolved (n=1) and resolving (n=1).

Post-marketing Sources (Including Spontaneous and Solicited) Primary Dose Cases

During the reporting period, 12 post-marketing sources (including spontaneous and solicited), initial, primary dose cases reporting multiple sclerosis, including optic neuritis were retrieved. These 12 initial, post-marketing, primary dose cases reported 12 serious EOI.

Cumulatively, 67 (33 medically confirmed and 34 medically unconfirmed) post-marketing, primary dose cases reporting multiple sclerosis, including optic neuritis were identified. All 67 cases were serious and reported a total of 69 serious EOI.

Of these 12 post-marketing, initial, primary dose cases, the most frequently reported countries/territories of origin (≥2) were Germany (n=4), followed by the US (n=3) and Poland (n=2). These cases concerned 7 males, 4 females, and 1 did not report sex. The age range was from 21 to 65 years.

The EOI included multiple sclerosis (n=5), multiple sclerosis relapse (n=4), and optic neuritis (n=3). The mean and median TTO were 42.9 and 10 days, respectively. Where reported (n=7), the outcomes were not resolved (n=4), resolving (n=2), and resolved (n=1).

Table 134: Frequency of MedDRA PTs of Interest in Post-marketing, Primary Dose Cases Reporting Multiple Sclerosis, Including Optic Neuritis With the Use of Ad26.COV2.S

MedDRA PTs	Number of Serious Events Reported During the Interval Reporting Period[a]	Number of Serious Events Reported Cumulatively
Multiple sclerosis	5	33
Multiple sclerosis relapse	4	10
Optic neuritis	3	25

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: The MedDRA PTs of interest have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022).

There was no fatal post-marketing, initial, primary dose cases retrieved from the search of the Company global safety database during the interval reporting period.

Booster Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 5 (3 medically confirmed and 2 medically unconfirmed) initial cases reported as booster were identified. All 5 cases were serious and reported a total of 7 serious EOI. Of these cases, 3 were heterologous and 2 were homologous. All 5 booster cases reported as booster during the interval were reported from post-marketing spontaneous sources. No cases were reported from Janssen Sponsored Clinical Studies or Janssen Supported Clinical Studies. Cumulatively, the aforementioned 5 (3 medically confirmed and 2 medically unconfirmed) cases reported as booster were identified.

Post-marketing Sources (Including Spontaneous and Solicited) Booster Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 5 post-marketing sources cases (spontaneous), initial cases reported as booster were retrieved. These 5 post-marketing, initial, booster dose cases reported 7 serious EOI. Cumulatively, the aforementioned 5 (3 medically confirmed). The reported countries/territories of origin in these post-marketing cases reported as booster were Germany (n=3), followed by Greece and the US (n=1 each). These cases concerned 4 males and 1 female. The age range was from 22 to 37 years. The EOI included optic neuritis (n=4) and multiple sclerosis (n=3). The mean and median TTO were 170.2 and 229 days, respectively. The reported outcomes were not resolved (n=5) and resolved with sequelae and resolving (n=1 each).

Table 136: Frequency of MedDRA PTs of Interest in Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Multiple Sclerosis, Including Optic Neuritis

MedDRA PTs	Number of Serious Events Reported During the Interval Reporting Period[a]	Number of Serious Events Reported Cumulatively
Optic neuritis	4	4
Multiple sclerosis	3	3

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

a: The MedDRA PTs of interest have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event of interest.

There were no fatal post-marketing initial cases reported as booster which were retrieved from the search of the Company global safety database during the interval reporting period.

Literature ICSR

No information was identified that would change the characterisation of risk.

MAH Discussion

Review of the cases, including demographics, concomitant medications, concurrent conditions/medical history, outcome, and seriousness received during this reporting period is consistent with what is currently known about multiple sclerosis, including optic neuritis.

O/E Analysis Results

Since the previous PBRER data lock point (24 February 2022), the broad O/E ratio has remained <1 in the US and EU for both age groups. A restricted O/E analysis with sensitivity analysis was not required.

MAH Conclusion

Based on the evaluation of the cases, and review of safety from other sources, the information is consistent with the information known about multiple sclerosis, including optic neuritis. The Company will continue to closely monitor multiple sclerosis, including optic neuritis as an AESI.

Rapporteur assessment comment:

This AESI has been evaluated in depth in the MSSRs 6-9 including a time frame up to March 2022 and no new safety information has been identified in these reports. No additional safety concern is raised in this PSUR.

Narcolepsy

Narcolepsy is listed as an AESI in the cRMP, EU RMP, and the US PVP. In the PRAC assessment for the PBRER covering the reporting period from 25 August 2021 to 24 February 2022, the rapporteur concluded that, narcolepsy is an event which will take long to be identified, thus required the Company to be monitor and present the topic in upcoming PBRERs and to "*focus on cases that could be true cases of narcolepsy*".

Primary Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 126 (14 medically confirmed and 112 medically unconfirmed) initial, primary dose cases reporting narcolepsy were identified. Of these 126 cases, 41 were serious and 85 were nonserious and reported a total of 133 EOI (29 serious; 104 nonserious). All 126 primary dose cases received during the interval reporting period were reported from post-marketing sources (including spontaneous and solicited). No cases were reported from Janssen Sponsored Clinical Studies or Janssen Supported Clinical Studies. Cumulatively, 564 (77 medically confirmed and 487 medically unconfirmed) primary dose cases reporting narcolepsy were identified. Of these cases, 183 were serious and 381 were nonserious and reported a total of 572 EOI (91 serious; 481 nonserious). Of the 564 cumulative primary dose cases received, 1 was reported from a Janssen Supported Clinical Study and 563 were from post-marketing sources. No cases were reported from Janssen Sponsored Clinical Studies.

Post-marketing Sources (Including Spontaneous and Solicited) Primary Dose Cases

During the reporting period, 126 post-marketing sources (including spontaneous and solicited), initial, primary dose cases reporting narcolepsy were retrieved. These 126 post-marketing, initial, primary dose cases reported 133 EOI (29 serious; 104 nonserious).

Cumulatively, 563 (76 medically confirmed and 487 medically unconfirmed) post-marketing, primary dose cases reporting narcolepsy were identified. Of these cases, 183 were serious and 380 were nonserious and reported a total of 571 EOI (91 serious; 480 nonserious). Of these 126 post-marketing, initial primary dose cases, the most frequently reported countries/territories of origin (≥9) were Germany (n=80), followed by the US (n=11), and Poland (n=9). These cases concerned 65 males, 59 females, and 2 did not report sex. The age range was from 18 to 78 years.

The EOI included sleep disorder (n=117), hypersomnia (n=15), and sudden onset of sleep (n=1). The mean and median TTO were 8.9 days and 1 day, respectively. Where reported (n=117), the outcomes were not resolved (n=61), resolving (n=28), resolved (n=21), and resolved with sequelae (n=7).

Table 138: Frequency of MedDRA PTs of Interest in Post-marketing, Primary Dose Cases Reporting Narcolepsy With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Sleep disorder	26	91	69	270
Hypersomnia	2	13	18	210
Sudden onset of sleep	1	0	1	0

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

a: The MedDRA PTs of interest have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event of interest.

Fatal Post-marketing Primary Dose Cases

During the reporting period, 1 post-marketing, initial, primary dose fatal case with no fatal EOI was retrieved.

Booster Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 14 initial cases reported as booster were identified. There were 4 serious and 10 nonserious cases and reported a total of 15 EOI (1 serious; 14 nonserious). Of these cases, 10 were heterologous and 4 were homologous. All 14 initial cases reported as booster during the interval were from post-marketing sources (including spontaneous and solicited). No cases were reported from Janssen Sponsored Clinical Studies or Janssen Supported Clinical Studies. Cumulatively, 31 (3 medically confirmed and 28 medically unconfirmed) cases reported as booster were identified. Of these cases, 11 were serious and 20 were nonserious and reported a total of 32 EOI (4 serious; 28 nonserious). Of these cases, 16 were heterologous and 15 were homologous. All 31 cumulative booster dose cases received were reported from post-marketing sources (including spontaneous and solicited cases). No cases were reported from Janssen Sponsored Clinical Studies or Janssen Supported Clinical Studies.

Post-marketing Sources (Including Spontaneous and Solicited) Booster Dose Cases

During the reporting period, 14 post-marketing sources (including spontaneous and solicited), initial cases reported as booster were retrieved. These 14 post-marketing, initial, booster dose cases reported 15 EOI (1 serious; 14 nonserious). Cumulatively, 31 (3 medically confirmed and 28 medically unconfirmed) post-marketing cases reported as booster were identified. Of these cases, 11 were serious and 20 were nonserious and reported a total of 32 EOI (4 serious; 28 nonserious). Of these 14 post-marketing, initial cases reported as booster, the most frequently reported countries/territories of origin (≥2) were Germany (n=9), followed by Austria and Brazil (n=2 each). These cases concerned 9 females and 5 males. The age range was from 20 to 59 years.

The EOI included sleep disorder (n=13) and hypersomnia (n=2). The mean and median TTO were 100.2 and 2 days, respectively. The reported outcomes were not resolved (n=12), resolving (n=2), and resolved with sequelae (n=1).

Table 140: Frequency of MedDRA PTs of Interest in Post-marketing Cases Reported as Booster Dose With the Use of Ad26.COV2.S and Reporting Narcolepsy

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Sleep disorder	1	12	3	18
Hypersomnia	0	2	1	10

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

a: The MedDRA PTs of interest have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event of interest.

There were no initial, fatal cases reported as booster which were retrieved from the search of the Company global safety database during the interval reporting period.

Literature ICSR

No information was identified that would change the characterisation of risk.

MAH Discussion

Upon review of the interval and cumulative data, no new safety information was identified regarding this AESI. Most of the cases reported hypersomnia and sleep disorder, which are not indicative of narcolepsy.

O/E Analysis Results

No cases meeting the definition of narcolepsy have been identified during the reporting period. Therefore, no O/E analysis was performed for this AESI.

MAH Conclusion

Based on the evaluation of the cases, and review of safety from other sources, the information is consistent with the information known about narcolepsy. The Company will continue to closely monitor narcolepsy as an AESI.

Rapporteur assessment comment:

During the interval reporting period of 25 February 2022 to 24 August 2022, 126 (14 medically confirmed and 112 medically unconfirmed) initial, primary dose cases reporting narcolepsy were identified (all post-marketing). Of these 126 cases, 41 were serious and 85 were nonserious and reported a total of 133 EOI (29 serious; 104 nonserious). The most common reported EOI was sleep disorder (n=117, of which 91 were non-serious). For booster dose, 14 initial cases (all post-marketing) were reported (4 serious and 10 nonserious). Of these cases, 10 were heterologous and 4 were homologous. Majority of the booster dose cases were sleep disorder (n=13).

During the reporting interval, no cases met the definition of narcolepsy. For the coming PSUR, the MAH should continue to focus on cases that could be true cases of narcolepsy.

Sensorineural Hearing Loss

Sensorineural hearing loss (SNHL) is listed as an AESI in the cRMP, EU RMP, and the US PVP.

According to the PRAC FAR (PRAC AR 2022) for the Ad26.COV2.S PBRER EMEA/H/C/PSUSA/00010916/202202) received on 29 September 2022: *"Removing tinnitus from the search strategy is endorsed."*

Primary Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 56 (11 medically confirmed and 45 medically unconfirmed) initial, primary dose cases reporting SNHL were identified. Of these 56 cases, 43 were serious and 13 were nonserious and reported a total of 58 EOI (44 serious; 14 nonserious). Of these 56 primary dose cases received during the interval reporting period, 1 was reported from a Janssen Sponsored Clinical Study and 55 were from post-marketing sources (including spontaneous and solicited). No cases were reported from Janssen Supported Clinical Studies. Cumulatively, 234 (55 medically confirmed and 179 medically unconfirmed) primary dose cases reporting SNHL were identified. Of these cases, 176 were serious and 58 were nonserious and reported a total of 244 EOI (174 serious; 70 nonserious). Of the 234 cumulative primary dose cases received, 2 were reported from Janssen Sponsored Clinical Studies, 1 was from a Janssen Supported Clinical Study, and 231 were from post-marketing sources (including spontaneous and solicited cases).

Janssen Sponsored Clinical Studies Primary Dose Cases

During the reporting period, 1 initial, primary dose case reporting SNHL was retrieved from a Janssen Sponsored Clinical Study. This case was from VAC31518COV3009 and concerned a 50-year-old male from [redacted] who experienced a serious EOI of deafness neurosensory. The reported TTO was 252 days and the reported outcome was not resolved.

Post-marketing Sources (Including Spontaneous and Solicited) Primary Dose Cases

During the reporting period, 55 post-marketing sources (including spontaneous and solicited), initial, primary dose cases reporting SNHL were retrieved. These 55 post-marketing, primary dose cases

reported 57 EOI (43 serious; 14 nonserious). Cumulatively, 231 (52 medically confirmed and 179 medically unconfirmed) post-marketing, primary dose cases reporting SNHL were identified. Of these cases, 173 were serious and 58 were nonserious and reported a total of 241 EOI (171 serious; 70 nonserious). Of these 55 post-marketing, primary dose cases, the most frequently reported countries/territories of origin (≥5) were Germany (n=30), followed by the US (n=7) and France (n=5). These cases concerned 30 females, 22 males, and 3 did not report sex. The age range was from 19 to 90 years.

The EOI (≥3) included deafness (n=28), hypoacusis (n=16), deafness unilateral (n=5), and vestibular neuronitis (n=3). The mean and median TTO were 22.6 and 3 days respectively. Where reported (n=50), the outcomes were not resolved (n=27), resolving (n=12), resolved (n=6), and resolved with sequelae (n=5).

Table 142: Frequency of MedDRA PTs of Interest in Post-marketing, Primary Dose Cases Reporting Sensorineural Hearing Loss With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Deafness	28	0	80	0
Hypoacusis	4	12	34	63
Deafness unilateral	5	0	24	0
Vestibular neuronitis	3	0	14	1
Auditory disorder	0	2	2	6
Deafness bilateral	1	0	2	0
Deafness neurosensory	1	0	9	0
Deafness transitory	1	0	4	0

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

a: The MedDRA PTs of interest have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event of interest.

There were no initial, fatal post-marketing primary dose cases retrieved from the search of the Company global safety database during the interval reporting period.

Booster Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 8 initial cases (all medically unconfirmed cases) reported as booster were identified. Although 1 medically unconfirmed case was reported as a booster, it was determined to be a primary dose case upon further review and has been captured in the primary dose subsection above. Of the remaining 7 cases (all medically unconfirmed cases), 2 were serious and 5 were nonserious and reported a total of 7 EOI (2 serious; 5 nonserious). Of these cases, 3 were homologous and 4 were heterologous. All 7 initial cases reported as booster during the interval were from post-marketing sources (including spontaneous and solicited). No cases were reported from Janssen Sponsored Clinical Studies or Janssen Supported Clinical Studies. Cumulatively, 10 (no medically confirmed and 10 medically unconfirmed) cases reported as booster were identified. Of these cases, 5 were serious and 5 were nonserious and reported a total of 10 EOI (4 serious; 6 nonserious). Of these cases, 5 were homologous and 5 were heterologous. All 10 cumulative booster dose cases received were reported from post-marketing sources (including spontaneous and solicited cases). No cases were reported from Janssen Sponsored Clinical Studies or Janssen Supported Clinical Studies.

Post-marketing Sources (Including Spontaneous and Solicited) Booster Dose Cases

During the reporting period, 7 post-marketing sources (including spontaneous and solicited), initial cases reported as booster were retrieved. These 7 post-marketing, initial, booster dose cases reported 7 EOI (2 serious; 5 nonserious). Cumulatively, 10 (no medically confirmed and 10 medically unconfirmed) post-marketing cases reported as booster were identified. Of these cases, 5 were serious and 5 were nonserious and reported a total of 10 EOI (4 serious; 6 nonserious).

For these 7 post-marketing cases reported as booster, the reported countries/territories of origin were [redacted] (n=5), followed by [redacted] and [redacted] (n=1 each). These cases concerned 7 females. The age range was from 27 to 60 years.

The EOI included hypoacusis (n=5), and deafness unilateral and vestibular neuronitis (n=1 each). The mean and median TTO were 4.8 days and 0.5 day, respectively. Where reported (n=5), the outcomes were resolving (n=2), and not resolved, resolved, and resolved with sequelae (n=1 each).

Table 144: Frequency of MedDRA PTs of Interest in Post-marketing Cases Reported as Booster Dose With the Use of Ad26.COV2.S and Reporting Sensorineural Hearing Loss

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Hypoacusis	0	5	1	6
Deafness unilateral	1	0	1	0
Vestibular neuronitis	1	0	1	0

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: The MedDRA PTs of interest have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022).

There were no initial fatal cases reported as booster which were retrieved from the search of the Company global safety database during the reporting interval.

Literature ICSR

No information was identified that would change the characterisation of risk.

MAH Discussion

Most cases presented limited information for a meaningful medical assessment. Two primary dose cases specifically reported that the patient experienced SNHL during this interval, 1 from a Janssen Sponsored Clinical Study, and 1 from a spontaneous literature report. In the case from the Janssen Sponsored Clinical Study, the EOI was outside the 60-day risk window. In the literature case, the patient experienced sudden SNHL 7 days post-vaccination. Incomplete audiogram results were provided in this case, and baseline data was missing. Additionally, the authors of the article concluded that the findings of their study did not suggest an association between COVID-19 vaccination and an increased incidence of hearing loss compared with the expected incidence in the general population.

O/E Analysis Results

Table 145: Sensorineural Hearing Loss w/o Tinnitus, Tinnitus: Restricted O/E and Sensitivity Analysis Results (Cumulative Through 24 August 2022)

	Restricted 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	US (1 to 21)	18 to 59	24.89	0.11	(0.07, 0.16)	0.52	(0.33, 0.76)
	US (1to 14)	18 to 59	20.89	0.13	(0.08, 0.20)	0.65	(0.40, 1.00)
Sensorineural Hearing Loss	EU (1 to 21)	18 to 59	44.68	0.16	(0.12, 0.22)	0.81	(0.59, 1.09)
	EU (1 to 14)	18 to 59	40.76	0.23	(0.16, 0.31)	1.11	(0.80, 1.51)

Key: AESI=Adverse Events of Special Interest; CI=Confidence Interval; EOI=Event(s) of Interest; EU=European Union; LB=Lower Bound; O/E=Observed versus Expected; PE=Point Estimate; PT=Preferred Term; RP=Reporting Percentage; US=United States; W/O=Without
a: Counts included EOI (from valid cases) that occurred within the risk window (Day: 1 to 21, 1 to 14) only.
b: Poisson exact confidence interval (95% CI).

Sensorineural Hearing Loss *w/o Tinnitus*

The EU restricted sensitivity analysis showed an O/E ratio of >1 in the 18 to 59 age group (risk window: 1 to 14 days) only. However, the O/E ratio was not statistically significant (lower bound of 95% confidence interval >1). The O/E ratio was <1 for the US and for the EU over 60 age group in the restricted analysis for both risk windows.

MAH Conclusion

Based on the evaluation of the cases and review of safety from other sources, the information is consistent with the information known about SNHL. With the exception of transient tinnitus (listed as an ADR for Ad26.COV2.S) no trends have been identified regarding vestibulocochlear disorders since the launch of the vaccine. The current available evidence is considered insufficient to establish a causal link between the vaccine and SNHL. The Company proposes to monitor this event through routine pharmacovigilance activities.

Rapporteur assessment comment:

During the reporting period of 25 February 2022 to 24 August 2022, 55 cases reporting SNHL were retrieved from post-marketing sources and one case of SNHL was reported from a Janssen sponsored clinical study (primary dose). The majority of cases (n=28) reported deafness. In addition, eight initial cases of SNHL reported as booster dose was also identified. The frequency of SNHL has clearly decreased from last PSUR, which is due to the removal of tinnitus from the search strategy (tinnitus is already listed in the SmPC section 4.8 at frequency rare). All restricted O/E ratios were <1. The O/E ratio for the sensitivity analysis was 1,1 (CI: 0,8-1,5) for the EU risk window 1-14 age group 18-59 years.

No new safety concern is detected here.

Transverse Myelitis

Transverse myelitis is listed as an AESI in the cRMP, EU RMP, and the US PVP.

Primary Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 16 (7 medically confirmed and 9 medically unconfirmed), initial, primary dose cases reporting transverse myelitis were identified. All 16 cases were serious and reported a total of 16 serious EOI. All 16 initial, primary dose cases received during the interval reporting period were reported from post-marketing sources (including spontaneous and solicited cases). No cases were reported from Janssen Sponsored Clinical Studies or Janssen Supported Clinical Studies. Cumulatively, 112 (75 medically confirmed and 37 medically unconfirmed) primary dose cases reporting transverse myelitis were identified. All 112 cases were serious and reported a total of 127 serious EOI. Of the 112 cumulative, primary dose cases received, 1 was reported from a Janssen Sponsored Clinical Study, 2 from Janssen Supported Clinical Studies, and 109 from post-marketing sources.

Post-marketing Sources (Including Spontaneous and Solicited) Primary Dose Cases

During the reporting period, 16 post-marketing sources (including spontaneous and solicited), initial, primary dose cases reporting transverse myelitis were retrieved. These 16 post-marketing, initial, primary dose cases reported 16 serious EOI. Cumulatively, 109 (72 medically confirmed and 37 medically unconfirmed) post-marketing, primary dose cases reporting transverse myelitis were identified. All 109 cases were serious and reported a total of 124 serious EOI.

Of these 16 post-marketing, initial primary dose cases, the most frequently reported countries/territories of origin (≥5) were Germany (n=6), followed by the US (n=5). These cases concerned 9 males, 3 females, and 4 did not report sex. The age range was from 25 to 67 years. The EOI included myelitis, myelitis transverse (n=7 each), and neuromyelitis optica spectrum disorder (n=2). The mean and median TTO were 15 and 14 days, respectively. Where reported (n=10), the outcomes were not resolved (n=9) and resolving (n=1).

Table 147: Frequency of MedDRA PTs of Interest in Post-marketing, Primary Dose Cases Reporting Transverse Myelitis With the Use of Ad26.COV2.S

MedDRA PTs	Number of Serious Events Reported During the Interval Reporting Period[a]	Number of Serious Events Reported Cumulatively
Myelitis	7	27
Myelitis transverse	7	63
Neuromyelitis optica spectrum disorder	2	7

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: The MedDRA PTs of interest have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022).

There were no initial, fatal, post-marketing primary dose cases retrieved from the search of the Company global safety database during the interval reporting period of 25 February 2022 to 24 August 2022.

Booster Dose

During the interval reporting period of 25 February 2022 to 24 August 2022 and cumulatively, 3 (2 medically confirmed and 1 medically unconfirmed) initial cases reported as booster were identified. All 3 cases were serious and reported a total of 3 serious EOI. Of these cases, 2 were heterologous and 1 was homologous. All 3 cases reported as booster during the interval and cumulatively, were reported from post-marketing spontaneous sources. No cases were reported from Janssen Sponsored or Supported Clinical Studies.

Post-marketing Sources (Including Spontaneous and Solicited) Booster Dose Cases

During the reporting period and cumulatively, 3 post-marketing sources (including spontaneous and solicited), initial cases reported as booster were retrieved. These 3 post-marketing, initial, booster dose cases reported 3 serious EOI. The reported countries/territories of origin in these 3 cases reported as booster were [redacted] (n=1 each). All 3 cases concerned females. The age range was from 39 to 67 years. The EOI included myelitis transverse (n=2) and demyelination (n=1). The mean and median TTO were 80.7 and 101 days, respectively. Where reported (n=2), the outcomes were not resolved and resolved with sequelae (n=1 each).

Fatal Post-marketing Booster Dose Cases

There were no initial, fatal cases reported as booster which were retrieved from the search of the Company global safety database during the interval reporting period.

Literature ICSR

No information was identified that would change the characterisation of risk.

O/E Analysis Results

Table 148: Transverse Myelitis: Restricted O/E and Sensitivity Analysis Results (Cumulative Through 24 August 2022)

Restricted 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	33.00	2.06	(1.42, 2.89)	4.11	(2.83, 5.78)
	≥60	8.00	1.42	(0.61, 2.79)	2.83	(1.22, 5.58)
EU	18 to 59	20.92	2.71	(1.68, 4.15)	19.00	(11.75, 29.06)
	≥60	2.08	5.84	(0.75, 20.65)	31.16	(4.01, 110.12)

Key: CI=Confidence Interval; EOI=Event(s) of Interest; EU=European Union; LB=Lower Bound; O/E=Observed versus Expected; PE=Point Estimate; RP=Reporting Percentage; US=United States

a: Counts included EOI (from valid cases) that occurred within the risk window (Day: 1 to 42) only.

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

The restricted sensitivity analysis showed an O/E ratio of >1 in both age groups in both regions. The O/E ratio was statistically significant above 1 (lower bound of 95% confidence interval >1) for all groups.

MAH Conclusion

Based on the evaluation of the cases, and review of safety from other sources, the information is consistent with the information known about transverse myelitis. The Company will continue to closely monitor transverse myelitis as an AESI.

Rapporteur assessment comment:

Transverse myelitis has been listed in section 4.4 and 4.8 in the SmPC based on in depth analyses performed in SSRs, and a subsequent variation (II-35). No new information requiring additional regulatory actions was identified during the reporting period.

Vascular Disorders

Cerebrovascular Events

Cerebrovascular events are listed as an AESI in the cRMP, EU RMP, and the US PVP.

Primary Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 242 (158 medically confirmed and 84 medically unconfirmed) initial, primary dose cases reporting cerebrovascular events were identified. Of these 242 cases, 240 were serious and 2 were nonserious and reported a total of 288 EOI (285 serious; 3 nonserious). Of these 242 initial, primary dose cases received during the interval reporting period, 51 were reported from Janssen Sponsored Clinical Studies, 1 from a Janssen Supported Clinical Study, and 190 from post-marketing sources (including spontaneous and solicited). Cumulatively, 1,693 (1,064 medically confirmed and 629 medically unconfirmed) primary dose cases reporting cerebrovascular events were identified. Of these cases, 1,682 were serious and 11 were nonserious and reported a total of 2,267 EOI (2,252 serious; 15 nonserious). Of the 1,693 cumulative primary dose cases received, 160 were reported from Janssen Sponsored Clinical Studies, 16 from Janssen Supported Clinical Studies, and 1,517 from post-marketing sources (including spontaneous and solicited cases).

Janssen Sponsored Clinical Studies Primary Dose Cases

During the reporting period, 51 initial, primary dose cases reporting cerebrovascular events were retrieved from Janssen Sponsored Clinical Studies. Of these 51 cases, 40 were from VAC31518COV3001, 9 from VAC31518COV3009, and 1 each from VAC31518COV1001 and VAC31518COV2008. These 51

cases reported 54 EOI (52 serious; 2 nonserious). Of these 51 cases, the most frequently reported countries/territories of origin were the US (n=29), followed by South Africa (n=8) and Brazil (n=6). These cases concerned 28 males and 23 females. The age range was from 46 to 89 years. The EOI (≥4) included transient ischaemic attack (n=12), ischaemic stroke (n=10), cerebrovascular accident (n=9), and cerebral infarction (n=4). The mean and median TTO were 396.7 and 418 days, respectively. Where reported (n=53), the outcomes were resolved (n=25), resolving (n=10), fatal (n=7), resolved with sequelae (n=6), and not resolved (n=5).

Janssen Supported Clinical Studies Primary Dose Cases

One initial, primary dose case reporting cerebrovascular events was retrieved from a Janssen Supported Clinical Study. This case was from VAC31518COV3021 and concerned an 84-year-old male from South Africa. This case reported a serious EOI of cerebellar infarction. The reported TTO was 6 days, and the event outcome was reported as resolving.

Post-marketing Sources (Including Spontaneous and Solicited)

Primary Dose Cases During the reporting period, 190 post-marketing sources (including spontaneous and solicited), initial, primary dose cases reporting cerebrovascular events were retrieved. These 190, post-marketing, initial, primary dose cases reported 233 EOI (232 serious; 1 nonserious). Cumulatively, 1,517 (888 medically confirmed and 629 medically unconfirmed) post-marketing, primary dose cases reporting cerebrovascular events were identified. Of these cases, 1,515 were serious and 2 were nonserious and reported a total of 2,078 EOI (2,074 serious; 4 nonserious). Of these 190 post-marketing, initial, primary dose cases, the most frequently reported countries/territories of origin (≥26) were the US (n=77), followed by Germany (n=35) and Philippines (n=26). These cases concerned 95 males, 83 females, and 12 did not report sex. The age range was from 20 to 90 years.

Table 150: Frequency of MedDRA PTs of Interest in Post-marketing, Primary Dose Cases Reporting Cerebrovascular Events With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Cerebrovascular accident	62	0	619	0
Cerebral venous sinus thrombosis	24	0	142	0
Hemiparesis[b]	23	0	177	0
Cerebral infarction	17	0	102	0
Transient ischaemic attack	14	0	133	0
Cerebral haemorrhage	12	0	104	0
Ischaemic stroke	9	0	104	0
Cerebral venous thrombosis	8	0	40	0
Hemiplegia[b]	8	0	75	0
Cerebrovascular disorder	5	1	11	2
Cerebral thrombosis	5	0	79	0
Haemorrhagic stroke	5	0	34	0
Hemihypoaesthesia[b]	5	0	8	0

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

a: The MedDRA PTs of interest with a frequency ≥5 have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event of interest.

b: Included MedDRA PTs associated with central nervous system haemorrhages and cerebrovascular accidents. When reported as the only PTs, may not be indicative of central nervous system haemorrhages and cerebrovascular accidents.

The EOI (≥23) included cerebrovascular accident (n=62), cerebral venous sinus thrombosis (n=24), and hemiparesis (n=23). The mean and median TTO were 91.4 and 41 days, respectively. Where reported (n=144), the outcomes were not resolved (n=62), resolved (n=27), resolving (n=26), fatal (n=21), and resolved with sequelae (n=8).

Non-Fatal Cases in Patients ≤ 40 Years of Age

There was a total of 36 non-fatal cases that occurred in patients ≤40 years of age from post-marketing sources. Two of the non-fatal cases involved a haemorrhagic event. Of the 36 non-fatal cases, the EOI was outside the 28-day risk window in 8 cases. Of the remaining 28 cases, 3 were confounded by the patients' medical history and/or concurrent diseases. Of the remaining 25 cases, all lacked relevant details, including TTO, medical history, concomitant medications, and diagnostic test results. 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 cerebrovascular events being causally associated with Ad26.COV2.S.

Fatal Post-marketing Primary Dose Cases

During the reporting period, 23 post-marketing, initial, primary dose fatal cases with a total of 34 events were retrieved. Of these 23 cases, 17 reported 21 fatal EOI. The fatal EOI (≥2) in the 17 cases were cerebrovascular accident (n=6), cerebral haemorrhage (n=4), ischaemic stroke (n=3), cerebral thrombosis, and hemiparesis (n=2 each).

Of the 17 fatal cases, 13 occurred in patients ≥41 years of age and 4 occurred in patients ≤40 years of age. Of the 13 cases, the EOI was outside the 28-day risk window in 8 cases. Of the remaining 5 cases, 3 were confounded by the patients' medical history and/or concurrent diseases. The remaining 2 cases lacked relevant details, including TTO, medical history, concomitant medications, and diagnostic test results.

Booster Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 22 (14 medically confirmed and 8 medically unconfirmed) initial cases reported as booster were identified. Although 1 case was reported as booster, it was determined to be a primary dose case upon further review and has been captured in the primary dose subsection above. All of the remaining 21 (14 medically confirmed and 7 medically unconfirmed) cases were serious and reported a total of 24 EOI (23 serious; 1 nonserious). Of these cases, 11 were heterologous and 10 were homologous.

Of these 21 initial cases reported as booster during the interval, 1 was reported from a Janssen Sponsored Clinical Study (VAC31518COV3001 and concerned a 57-year-old female from [redacted] who reported 1 serious EOI of cerebrovascular accident with TTO of 156 days and the event resolved) and 20 from post-marketing sources (including spontaneous and solicited). No cases were reported from Janssen Supported Clinical Studies. Cumulatively, 41 (24 medically confirmed and 17 medically unconfirmed) cases reported as booster were identified. All 41 cases were serious and reported a total of 52 EOI (51 serious; 1 nonserious). Of these cases, 27 were homologous and 14 were heterologous. Of the 41 cumulative booster cases received, 1 was reported from a Janssen Sponsored Clinical Study and 40 from post-marketing sources (including spontaneous and solicited). No cases were reported from Janssen Supported Clinical Studies.

Post-marketing Sources (Including Spontaneous and Solicited) Booster Dose Cases

During the reporting period, 20 post-marketing sources (including spontaneous and solicited), initial cases reported as booster were retrieved. These 20 post-marketing, initial, booster dose cases reported 23 EOI (22 serious; 1 nonserious). Cumulatively, 40 (23 medically confirmed and 17 medically unconfirmed) post-marketing cases reported as booster were identified. All 40 cases were serious and reported a total of 51 EOI (50 serious; 1 nonserious).

Of these 20 post-marketing, initial cases reported as booster, the most frequently reported countries/territories of origin (≥4) were the US (n=7), followed by Brazil and Germany (n=4 each). These cases concerned 11 males and 9 females. The age range was from 19 to 93 years. A single case may contain more than 1 EOI. The EOI (≥2) included cerebral thrombosis, cerebral venous sinus thrombosis,

cerebrovascular accident, hemiparesis, and subarachnoid haemorrhage (n=2 each). The mean and median TTO were 98.6 and 48 days, respectively. Where reported (n=17), the outcomes were not resolved (n=6), fatal and resolved (n=4 each), resolved with sequelae (n=2), and resolving (n=1).

Table 152: Frequency of MedDRA PTs of Interest in Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Cerebrovascular Events

MedDRA PTs	Number of Serious Events Reported During the Interval Reporting Period[a]	Number of Serious Events Reported Cumulatively
Cerebral thrombosis	2	3
Cerebral venous sinus thrombosis	2	3
Cerebrovascular accident	2	16
Hemiparesis	2	3
Subarachnoid haemorrhage	2	3

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

a: The MedDRA PTs of interest with a frequency ≥2 have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event of interest.

Fatal Post-marketing Booster Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 3 initial, fatal cases reported as booster cases with a total of 12 events were retrieved. Of these 3 cases, 2 reported 4 fatal EOI. The fatal EOI in the 2 cases were subarachnoid haemorrhage (n=2), intraventricular haemorrhage (n=1), and intracranial aneurysm (n=1). Of the 2 fatal cases, 1 occurred in a patient ≥41 years of age and 1 occurred in a patient ≤40 years of age. Both cases were heterologous booster cases. The case that occurred in the patient ≥41 years of age was outside the 28-day risk window and lacked relevant details. The case that occurred in the patient ≤40 years of age is summarised below:

This case (PHIFDA ID: [redacted]) concerned a 27-year-old male who experienced intraventricular and subarachnoid haemorrhage with uncal herniation on Day 251 following primary vaccination with Ad26.COV2.S and Day 100 following booster vaccination with the Pfizer BioNTech BNT162b2 COVID-19 vaccine. It was unknown whether the patient had any AEs following primary vaccination. On an unspecified date, the patient was hospitalised, experienced severe headache, vomiting, and generalised body weakness. The cause of death was intraventricular and subarachnoid haemorrhage with uncal herniation. It was unspecified whether an autopsy was performed or not.

MAH Comment: The lack of available information (specifically medical history, concomitant medications, and laboratory and diagnostic test results) precludes a meaningful medical assessment, however, given the long time to onset, a causal link to Ad26.COV2.S is unlikely.

Literature ICSR

No information was identified that would change the characterisation of risk.

O/E Analysis Results

Cerebrovascular Events -Haemorrhagic

Table 153: Cerebrovascular Events - Haemorrhagic: Restricted O/E and Sensitivity Analysis Results (Cumulative Through 24 August 2022)

Restricted 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	Female	18 to 29	9.23	0.35	(0.16, 0.66)	3.06	(1.42, 5.76)
		30 to 39	13.33	0.37	(0.20, 0.64)	4.85	(2.61, 8.24)
		40 to 49	30.37	0.63	(0.43, 0.90)	10.26	(6.94, 14.62)
		50 to 64	59.74	0.42	(0.32, 0.54)	6.83	(5.21, 8.80)
		65 to 74	34.92	0.30	(0.21, 0.42)	3.33	(2.32, 4.63)
		≥75	32.16	0.21	(0.14, 0.30)	2.63	(1.80, 3.70)
	Male	18 to 29	1.61	0.03	(0.00, 0.14)	0.27	(0.02, 1.12)
		30 to 39	9.65	0.17	(0.08, 0.31)	2.02	(0.95, 3.75)
		40 to 49	20.81	0.28	(0.17, 0.43)	4.49	(2.77, 6.88)
		50 to 64	62.73	0.29	(0.22, 0.37)	4.54	(3.49, 5.81)
		65 to 74	31.06	0.20	(0.14, 0.29)	1.84	(1.25, 2.61)
		≥75	21.30	0.16	(0.10, 0.25)	2.22	(1.38, 3.38)
EU	Female	18 to 29	5.27	2.08	(0.70, 4.76)	11.82	(3.98, 27.01)
		30 to 39	2.21	0.61	(0.09, 2.08)	2.55	(0.36, 8.72)
		40 to 49	9.21	0.96	(0.44, 1.81)	2.92	(1.35, 5.50)
		50 to 64	12.82	0.38	(0.20, 0.65)	1.02	(0.54, 1.74)
	Male	18 to 29	6.00	2.04	(0.75, 4.45)	10.67	(3.92, 23.22)
		30 to 39	7.00	0.87	(0.35, 1.79)	2.89	(1.16, 5.95)
		40 to 49	4.00	0.25	(0.07, 0.64)	0.68	(0.19, 1.75)

Key: CI=Confidence Interval; EOI=Event(s) of Interest; EU=European Union; LB=Lower Bound; O/E=Observed versus Expected; PE=Point Estimate; RP=Reporting Percentage; US=United States

a: Counts included EOI (from valid cases) that occurred within the risk window (Day: 1 to 28) only.

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

The US restricted sensitivity analysis showed an O/E ratio of >1 in the US for all female and all male age groups concerned except the male: 18 to 29 age group. Of these, the O/E ratio was statistically significant above 1 (lower bound of 95% confidence interval >1) in all female age groups and in all male age groups except the male 30 to 39 age group. The EU restricted sensitivity analysis showed an O/E ratio of >1 for all female and all male age groups concerned except the male 40 to 49 age group. Of these, the O/E ratio was statistically significant above 1 (lower bound of 95% confidence interval >1) for the female 18 to 29, 40 to

49 and male 18 to 29 and 30 to 39 age groups. Since the previous PBRER DLP (24 February2022), for the EU female 50 to 64 age group, the restricted sensitivity O/E ratio showed an increase from <1 to >1. The O/E ratio was not statistically significant above 1 (lower bound of 95% confidence interval >1).

Cerebrovascular Events - Non-Haemorrhagic

Table 154: Cerebrovascular Events – Non-Haemorrhagic: Restricted O/E and Sensitivity Analysis Results (Cumulative Through 24 August 2022)

Restricted 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	Female	18 to 29	9.44	0.26	(0.12, 0.48)	3.37	(1.57, 6.30)
		30 to 39	17.64	0.21	(0.12, 0.33)	4.33	(2.55, 6.88)
		40 to 49	41.70	0.31	(0.22, 0.42)	7.41	(5.33, 10.03)
		50 to 64	70.43	0.15	(0.12, 0.19)	4.42	(3.45, 5.58)
		65 to 74	38.21	0.09	(0.07, 0.13)	1.28	(0.91, 1.76)
		≥75	50.32	0.09	(0.07, 0.12)	1.17	(0.87, 1.54)
	Male	18 to 29	4.49	0.12	(0.04, 0.30)	1.34	(0.40, 3.26)
		30 to 39	13.52	0.12	(0.07, 0.21)	2.03	(1.10, 3.44)
		40 to 49	19.64	0.11	(0.07, 0.17)	1.94	(1.18, 3.01)
		50 to 64	83.38	0.13	(0.10, 0.16)	2.40	(1.91, 2.97)
		65 to 74	35.93	0.07	(0.05, 0.10)	0.81	(0.57, 1.12)
		≥75	24.24	0.06	(0.04, 0.09)	0.86	(0.55, 1.28)
EU	Female	18 to 29	6.27	0.68	(0.26, 1.46)	2.36	(0.89, 5.06)
		30 to 39	5.21	0.31	(0.10, 0.72)	0.89	(0.30, 2.04)
	Male	18 to 29	8.30	0.8	(0.35, 1.56)	2.74	(1.20, 5.33)
		30 to 39	12.23	0.74	(0.38, 1.28)	2.1	(1.09, 3.64)

Key: CI=Confidence Interval; EOI=Event(s) of Interest; EU=European Union; LB=Lower Bound; O/E=Observed versus Expected; PE=Point Estimate; RP=Reporting Percentage; US=United States

a: Counts included EOI (from valid cases) that occurred within the risk window (Day: 1 to 28) only.

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

The US restricted sensitivity analysis showed an O/E ratio of >1 for all female and all male age groups except the male 65 to 74 and ≥75 age groups. Of these, the O/E ratio was statistically significant above 1 (lower bound of 95% confidence interval >1) for all the female age groups except the 65 to 74 and the ≥75 age groups and for all the male age groups concerned except the 18 to 29 age group.

The EU restricted sensitivity analysis showed an O/E ratio of >1 for the female 18 to 29 and male 18 to 29 and 30 to 39 age groups. Of these, the O/E ratio was statistically significant above 1 (lower bound of 95% confidence interval >1) for the male age groups concerned.

MAH Conclusion

Based on the evaluation of the cases, and review of safety from other sources, the information is consistent with the information known about cerebrovascular events. The Company will continue to closely monitor cerebrovascular events as an AESI.

Rapporteur assessment comment:

During the interval reporting period of 25 February 2022 to 24 August 2022, 242 (158 medically confirmed and 84 medically unconfirmed) initial, primary dose cases reporting cerebrovascular events were identified. Of these, 240 were serious. Fifty-two of the cases were reported from Janssen clinical studies, most of them from US (n=29), and 190 were from post-marketing sources. The EOI (≥23) included cerebrovascular accident (n=62), cerebral venous sinus thrombosis (n=24), and hemiparesis (n=23). The mean and median TTO were 91.4 and 41 days, respectively.

During the reporting period, 21 (14 medically confirmed and 7 medically unconfirmed) initial cases reported as a booster dose were identified, all of them were serious and reported a total of 24 EOI (23 serious; 1 nonserious). Of these cases, 11 were heterologous and 10 were homologous. One of the cases were reported from a Janssen clinical study. Most of the post-marketing cases were reported from US.

The number of reported cerebrovascular events has decreased compared with the last PSUR period, which can be due to the decreased use of JCovden vaccine in EU and US. No new safety concern is detected here.

Disseminated Intravascular Coagulation

Disseminated intravascular coagulation (DIC) is listed as an AESI in the cRMP, EU RMP, and the US PVP.

Primary Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 3 (all medically confirmed) initial, primary dose cases reporting DIC were identified. All 3 cases were serious and reported a total of 3 serious EOI. All 3 initial, primary dose cases received during the interval reporting period were reported from post-marketing spontaneous sources. No cases were reported from Janssen Sponsored Clinical Studies and Janssen Supported Clinical Studies. Cumulatively, 26 (23 medically confirmed and 3 medically unconfirmed) primary dose cases reporting DIC were identified. All 26 cases were serious and reported a total of 26 serious EOI. All 26 cumulative, primary dose cases received were reported from post-marketing spontaneous sources. No cases were reported from Janssen Sponsored Clinical Studies or Janssen Supported Clinical Studies.

The 3 post-marketing, initial, primary dose cases reported 3 serious EOI. Cumulatively, 26 (23 medically confirmed and 3 medically unconfirmed) post-marketing, primary dose cases reporting DIC were identified. All 26 cases were serious and reported a total of 26 serious EOI. All 3 initial, primary dose cases retrieved were literature cases. Two were multiple patient cases from the Netherlands that discussed 3 females and 2 males, respectively with no age reported in either. The third case was a fatal concerning a 40-year-old male from Portugal.

The EOI included disseminated intravascular coagulation (n=3). The event outcome and TTO were not reported in any of the 3 cases.

One post-marketing, initial, primary dose fatal case with no fatal EOI was retrieved.

Booster Dose

There were no initial cases reported as booster which were retrieved from the search of the Company global safety database during the reporting interval. There were no cumulative cases reported as booster.

Literature ICSR

No information was identified that would change the characterisation of risk.

O/E Analysis Results

Since the previous PBRER O/E data lock point (24 February 2022), the broad O/E ratio has remained <1 in the US and EU for both age groups. A restricted O/E analysis with sensitivity analysis was therefore not required.

MAH Conclusion

Based on the evaluation of the cases, and review of safety from other sources, the information is consistent with the information known about DIC. The Company will continue to closely monitor DIC as an AESI.

Rapporteur assessment comment: No new safety concern is detected within DIC.

Hepatic Disorders

Acute hepatic failure is listed as an AESI in the cRMP, EU RMP, and the US PVP.

Primary Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 15 (12 medically confirmed and 3 medically unconfirmed) initial, primary dose cases reporting acute hepatic failure were identified. All 15 cases were serious and reported a total of 21 EOI (19 serious; 2 nonserious). Of these 15, 2 were reported from Janssen Sponsored Clinical Studies (VAC31518COV3001) and 13 from post-marketing spontaneous sources. No cases were reported from Janssen Supported Clinical Studies. Cumulatively, 95 (51 medically confirmed and 44 medically unconfirmed) primary dose cases reporting acute hepatic failure were identified. Of these cases, 88 were serious and 7 were nonserious and reported a total of 110 EOI (92 serious; 18 nonserious). Of the 95 cumulative, primary dose cases received, 10 were reported from Janssen Sponsored Clinical Studies, 2 from Janssen Supported Clinical Studies, and 83 from post-marketing spontaneous sources.

The two cases reported from study VAC31518COV3001 reported 2 serious EOI and were from [redacted] and [redacted] (n=1 each). One of these cases concerned a 66-year-old female and the other concerned a 44-year-old male. The EOI included hepatic cirrhosis (n=2). The mean and median TTO were 379.5 days each, respectively. The reported outcomes were not resolved and resolving (n=1 each).

The 13 post-marketing, initial, primary dose cases reported 19 EOI (17 serious; 2 nonserious). Cumulatively, 83 (39 medically confirmed and 44 medically unconfirmed) post-marketing, primary dose cases reporting acute hepatic failure were identified. Of these cases, 76 were serious and 7 were nonserious and reported a total of 98 EOI (80 serious; 18 nonserious). Of these 13 post-marketing, initial, primary dose cases, the most frequently reported countries/territories of origin (≥3) were the US (n=5), followed by the Philippines (n=3). These cases concerned 7 females and 6 males. The age range was from 27 to 72 years.

Table 158: Frequency of MedDRA PTs of Interest in Post-marketing, Primary Dose Cases Reporting Acute Hepatic Failure With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Liver disorder	3	1	5	10
Ascites	3	0	10	0
Hepatic cirrhosis	3	0	11	0
Hepatic failure	2	0	8	0
Hepatic steatosis	1	1	12	7
Acute hepatic failure	1	0	9	0
Drug-induced liver injury	1	0	2	0
Primary biliary cholangitis	1	0	1	0
Regenerative siderotic hepatic nodule	1	0	1	0
Varices oesophageal	1	0	2	0

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

a: The MedDRA PTs of interest have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event of interest.

The EOI (≥2) included liver disorder (n=4), ascites and hepatic cirrhosis (n=3 each), and hepatic failure and hepatic steatosis (n=2 each). The mean and median TTO were 151.3 and 209 days, respectively. Where reported (n=10), the outcomes were fatal and resolving (n=4 each), and not resolved (n=2).

Four post-marketing, initial, primary dose fatal cases with 4 fatal EOI were retrieved. The fatal EOI were hepatic failure (n=2), and acute hepatic failure and hepatic cirrhosis (n=1 each). The first case from Portugal reported from the literature source concerned a male in his 30's with concurrent conditions of obesity and smoking, who experienced severe abdominal pain which occurred 10 days following vaccination with Ad26.COV2.S. The patient was diagnosed with splenic/hepatic failure and a right femoral vein thrombosis. Post-operatively, the patient experienced multi-organ failure and subsequently died 48 hours after admission. An autopsy revealed the cause of death as vaccine induced immune thrombotic thrombocytopenia. The second fatal case from the US concerned a 56-year-old female with concurrent

conditions of hypertension and anxiety, who experienced malaise shortly following vaccination with Ad26.COV2.S and subsequently died due to worsening peripheral neuropathy, an unspecified autoimmune disorder, fall, kidney impairment, liver failure, and status post-implantation of an unspecified medical device. The fatal outcome occurred at an unspecified time following vaccination with Ad26.COV2.S. It was unspecified if an autopsy was performed. The third fatal case from the US concerned a 71-year-old male with a history of chronic urinary tract infections, diabetes mellitus, and renal stones who experienced fever, vomiting, chills, and was diagnosed with septic shock and thrombosis, approximately 48 hours after vaccination with Ad26.COV2.S. Subsequently, the patient's clinical course worsened, and the patient died 45 days following vaccination with Ad26.COV2.S. The causes of death included fever, septic shock, hepatic failure, hypotension, renal failure, thrombosis, and vomiting. It was unspecified if an autopsy was performed. The remaining case from the Philippines concerned a 59-year-old male who experienced the following with a fatal outcome: acute respiratory failure, alcoholic liver disease, decompensated hepatic cirrhosis, and upper gastrointestinal bleeding which occurred 344 days following Ad26.COV2.S vaccination. At the time of reporting, it was unspecified if an autopsy was performed.

Booster Dose

There were no initial, cases reported as booster which were retrieved from the search of the Company global safety database during the reporting period. Cumulatively, 2 (all medically unconfirmed) cases reported as booster were identified. Of these 2 cases, 1 was serious and 1 nonserious and reported a total of 2 nonserious EOI of liver disorder (n=2). Both cases were homologous. Both cumulative booster dose cases received were reported from post-marketing sources. No cases were reported from Janssen Sponsored Clinical Studies or Janssen Supported Clinical Studies.

Literature ICSR

ICSR literature cases received during the reporting period of 25 February 2022 to 24 August 2022 were reviewed, and no information was identified that would change the characterisation of risk.

O/E Analysis Results

Table 159: Acute Hepatic Failure: Restricted O/E Analysis with Sensitivity Analysis Results (Cumulative Through 24 August 2022)

	Restricted 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	13.00	4.42	(2.35, 7.56)	8.84	(4.71, 15.11)
	≥60	5.00	4.83	(1.57, 11.27)	9.65	(3.13, 22.53)

Key: CI=Confidence Interval; EOI=Event of Interest; LB=Lower Bound; O/E=Observed versus Expected; PE=Point Estimate; RP=Reporting Percentage; US=United States

a: Counts included EOI (from valid cases) that occurred within the risk window (Day: 1 to 14) only.

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

The US restricted sensitivity analysis showed an O/E ratio of >1 for both age groups. For both age groups, the O/E ratio was statistically significant above 1 (lower bound of 95% confidence interval >1).

MAH Conclusion

Based on the evaluation of the cases, and review of safety from other sources, the information is consistent with the information known about acute hepatic failure. The Company will continue to closely monitor acute hepatic failure as an AESI.

Rapporteur assessment comment:

An in-depth analysis of cumulative data regarding hepatic failure had been presented with the fifth MSSR (EMEA/H/C/005737/MEA/014.5). That review did not identify any particular support for direct vaccine

induced acute hepatic injury. Routine monitoring can continue. No new safety concern is detected here.

Renal Disorders

Acute kidney failure is listed as an AESI in the cRMP, EU RMP, and the US PVP.

Primary Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 26 (20 medically confirmed and 6 medically unconfirmed) initial, primary dose cases reporting acute kidney failure were identified. All 26 cases were serious and reported a total of 30 serious EOI. Of these 26 initial, primary dose cases received during the interval reporting period, 1 was reported from a Janssen Sponsored Clinical Study and 25 from post-marketing spontaneous sources. No cases were reported from Janssen Supported Clinical Studies. Cumulatively, 177 (135 medically confirmed and 42 medically unconfirmed) primary dose cases reporting acute kidney failure were identified. All 177 cases were serious and reported a total of 211 EOI (210 serious; 1 nonserious). Of the 177 cumulative, primary dose cases received, 19 were reported from Janssen Sponsored Clinical Studies, 2 from Janssen Supported Clinical Studies, and 156 from post-marketing sources (including spontaneous and solicited cases).

One of the initial, primary dose case reporting acute kidney failure was retrieved from a Janssen Sponsored Clinical Study. This case was from VAC31518COV3001 and concerned a 58-year-old male from [redacted] who reported a serious EOI of acute kidney injury. The TTO was 179 days and the outcome for the EOI was reported as resolving. There were no initial, primary dose cases retrieved from the search of the Company global safety Database.

During the period of 25 February 2022 to 24 August 2022, 25 post-marketing sources reported 29 serious EOI. The EOI (≥3) included acute kidney injury (n=13), renal impairment (n=7), and dialysis and renal failure (n=3 each). The mean and median TTO were 129.5 and 87 days, respectively. Where reported (n=25), the outcomes were fatal (n=16), not resolved and resolved (n=3 each), resolving (n=2), and resolved with sequelae (n=1).

Cumulatively, 156 (114 medically confirmed and 42 medically unconfirmed) post-marketing, primary dose cases reporting acute kidney failure were identified. All 156 cases were serious and reported a total of 190 EOI (189 serious; 1 nonserious). Of these 25 post-marketing, initial primary dose cases, the most frequently reported countries/territories of origin (≥3) were the US (n=16), followed by Germany and the Philippines (n=3 each). These cases concerned 17 males, 6 females, and 2 did not report sex. The age range was from 27 to 94 years.

Table 161: Frequency of MedDRA PTs of Interest in Post-marketing, Primary Dose Cases Reporting Acute Kidney Failure With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Acute kidney injury	13	0	91	0
Renal impairment	7	0	27	0
Dialysis	3	0	11	0
Renal failure	3	0	30	0
Anuria	1	0	8	0
Azotaemia	1	0	2	0
Haemodialysis	1	0	11	0

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

a: The MedDRA PTs of interest have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event of interest.

A total of 12 post-marketing cases reporting 16 fatal EOI were retrieved. The fatal EOI were acute kidney injury (n=8), dialysis (n=3), renal impairment (n=2), and anuria, azotaemia, and renal failure (n=1 each). All 12 cases were confounded by medical history or concurrent conditions that included infection

(n=7), including bacteraemia, COVID-19 infection, pneumonia, sepsis, and septic shock; diabetes (n=5); chronic kidney disease/end-stage renal disease (n=5); multi-system involvement (n=4); cardiac disease, including CAD/MI (n=2); congestive heart failure (n=2); and hepatic failure (2).

Booster Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 6 (3 medically confirmed and 3 medically unconfirmed) initial cases reported as booster were identified. All 6 cases were serious and reported a total of 6 serious EOI. Of these cases, 3 were heterologous and 3 were homologous. All 6 initial cases reported as booster during the interval were from post-marketing spontaneous sources. No cases were reported from Janssen Sponsored Clinical Studies or Janssen Supported Clinical Studies. Cumulatively, 8 (4 medically confirmed and 4 medically unconfirmed) cases reported as booster were identified. All 8 cases were serious and reported a total of 8 serious EOI. Of these cases, 4 were heterologous and 4 were homologous. All 8 cumulative, booster dose cases received were reported from post-marketing spontaneous sources. No cases were reported from Janssen Sponsored Clinical Studies or Janssen Supported Clinical Studies.

During the reporting period, 6 post-marketing, initial cases reported as booster were retrieved. These 6 cases reported 6 serious EOI. Cumulatively, 8 (4 medically confirmed and 4 medically unconfirmed) post-marketing cases reported as booster were identified. All 8 cases were serious and reported a total of 8 serious EOI. Of these 6 post-marketing, initial cases reported as booster, the most frequently reported country/territory of origin (n≥4) was the US (n=4). These cases concerned 4 males and 2 females. The age range was from 13 to 81 years.

Table 163: Frequency of MedDRA PTs of Interest in Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Acute Kidney Failure

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Acute kidney injury	3	0	4	0
Renal failure	2	0	3	0
Renal impairment	1	0	1	0

Table 163: Frequency of MedDRA PTs of Interest in Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Acute Kidney Failure

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious

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

a: The MedDRA PTs of interest have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022).

The EOI included acute kidney injury (n=3), renal failure (n=2), and renal impairment (n=1). The mean and median TTO was 146 and 73.5 days, respectively. Where reported (n=1), the outcome was not resolved (n=1).

There were no initial, fatal cases reported as booster during the reporting interval.

Literature ICSR

No information was identified that would change the characterisation of risk.

O/E Analysis Results

Table 164: Acute Kidney Failure: Restricted O/E and Sensitivity Analysis Results (Cumulative Through 24 August 2022)

Restricted 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	19.00	0.48	(0.29, 0.75)	1.03	(0.62, 1.62)

Key: CI=Confidence Interval; EOI=Event(s) of Interest; LB=Lower Bound; O/E=Observed versus Expected; PE=Point Estimate; RP=Reporting Percentage; US=United States

a: Counts included EOI (from valid cases) that occurred within the risk window (Day: 1 to 14) only.

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

The US restricted sensitivity analysis showed an O/E ratio of >1 in the ≥60 age group. The O/E ratio was not statistically significant above 1 (lower bound of 95% confidence interval <1).

MAH Conclusion

Based on the evaluation of the cases, and review of safety from other sources, the information is consistent with the information known about acute kidney failure. The Company will continue to closely monitor acute kidney failure as an AESI.

Rapporteur assessment comment:

During the interval reporting period of 25 February 2022 to 24 August 2022, 26 (20 medically confirmed and 6 medically unconfirmed) initial, primary dose cases reporting acute kidney failure were identified. In addition, 6 (3 medically confirmed and 3 medically unconfirmed) initial cases reported as booster were identified. All 26 cases were serious and reported a total of 30 serious EOI. The O/E ratio was around 1 in US subjects ≥60 years of age. No new safety concern is detected here.

Death

As per PRAC confirmation received in the PRAC FAR (PRAC AR 2022) for the Ad26.COV2.S PBRER (EMEA/H/C/PSUSA/00010916/202202): dated 29 September 2022: a separate death subsection with interval and cumulative death cases is no longer required to be presented in the report body of the current and future PBRERs.

Rapporteur assessment comment:

Noted.

2.4. Characterisation of risks

There are no new data that alter the characterisation of the safety profile.

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.

Data on long term efficacy are still missing. Currently there are no new data on efficacy that raises a concern.

4. Benefit-risk balance

JCOVDEN (Ad26.COV2.S, COVID-19 Vaccine Janssen) is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older. The use of this vaccine should be in accordance with official recommendations.

The vaccine is based on the initial Wuhan strain and has not been updated. Serious ADRs have been identified post marketing; occurring at different frequencies including TTS (very rare), venous thromboembolism (rare), ITP (not known), GBS (very rare), transverse myelitis (not known), CLS (not known) and cutaneous small vessel vasculitis, which have been reflected in the SmPC/PIL and evaluated mainly during the last PSUR intervals within a number of other procedures. Various events are still under further monitoring. These observations have led to the currently very limited use of this vaccine within the EU.

Based on the hitherto available data, the benefit/risk balance for COVID-19 vaccine Janssen remains unchanged.

5. Rapporteur Request for supplementary information

None

6. MAH responses to Request for supplementary information

N/A

Rapporteur assessment comment:

7. Comments from Member States

Member states' comments:
MS1 endorses the report

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Periodic Benefit Risk Evaluation Report

JNJ-78436735 (Ad26.COV2.S) Vaccine

Note: This report may contain unblinded clinical trial adverse event data

PERIOD COVERED BY THIS REPORT:
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I have reviewed this report and confirm that, to the best of my knowledge, it accurately describes the data available to date.

[redacted]

Electronic signatures have been applied at the end of the report.

EXECUTIVE SUMMARY

Introduction

This Periodic Benefit Risk Evaluation Report (PBRER) for JNJ-78436735 (Ad26.COV2.S), herein referred to as Ad26.COV2.S, summarises the safety data obtained by the Company from worldwide sources for the reporting period of 25 February 2022 to 24 August 2022. The content and format of this report follow the International Council for Harmonisation E2C guidelines on the PBRER and Module VII - Periodic Safety Update Reports (PSUR) of the European Medicines Agency (EMA) Guideline on Good Pharmacovigilance Practices, guidance from the EMA on the Consideration on Core Requirements for PSURs of coronavirus disease-2019 (COVID-19) vaccines,[1] and guidance outlined in EMA's Consideration on Core Requirements for Risk Management Plan of COVID-19 vaccine.[2] The International Birth Date of Ad26.COV2.S is based on the first regulatory approval in Bahrain on 25 February 2021.

Ad26.COV2.S is indicated for active immunisation for the prevention of COVID-19 in adults greater than or equal to 18 years of age. Ad26.COV2.S is administered as a colourless to slightly yellow, clear to very opalescent single dose suspension, for intramuscular injection. A booster dose (second dose) may be administered as a homologous booster dose intramuscularly at least 2 months after the primary vaccination in individuals 18 years of age and older. A booster dose may also be administered as a heterologous booster following the completion of a primary messenger ribonucleic COVID-19 vaccination, an adenoviral vector-based COVID-19 vaccine or an inactivated whole-virion COVID-19 vaccine. The dosing interval for the heterologous booster dose is the same as the dosing interval authorised for the booster dose of the vaccine administer for primary vaccination. The indication is as listed in the Company Core Data Sheet (CCDS) and represents the broadest Company-supported use.

Ad26.COV2.S is a monovalent vaccine composed of a recombinant, replication-incompetent human adenovirus type 26 (Ad26) vector, constructed to encode the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) spike (S) protein. Following vaccination, the S protein is expressed and stimulates an immune response. One dose of Ad26.COV2.S contains $5x10^{10}$ virus particles in 0.5 mL. Ad26.COV2.S is produced in the PER.C6® TetR Cell Line and by recombinant deoxyribonucleic acid technology. Ad26.COV2.S contains genetically modified organisms. Information regarding the pharmacodynamic and pharmacokinetic properties is contained in the appended CCDS.

Ad26.COV2.S contains the following excipients: citric acid monohydrate, trisodium citrate dihydrate, ethanol, 2-hydroxypropyl-β-cyclodextrin, polysorbate-80, sodium chloride, sodium hydroxide, hydrochloric acid, and water for injections (see Section 1, Introduction).

Worldwide Marketing Authorisation Status

Ad26.COV2.S is authorised in 108 countries/territories and import licences have been granted in 20 countries/territories worldwide (see Section 2, Worldwide Marketing Authorisation Status).

Exposure

Cumulative Exposure in Clinical Trials

Overall, an estimated 82,152 healthy subjects have been enroled in the Ad26.COV.S clinical programme, of which approximately 68,611 subjects have received Ad26.COV.S in the Company-sponsored

[1] EMA/362988/2021 (dated 08 July 2021)

[2] EMA/PRAC/709308/2022 (dated 01 September 2022)

interventional clinical trials. Of these, 580 subjects were exposed to Ad26.COV.S in the Phase 1 trials, 935 in a Phase 1/2a trial, 1,886 in the Phase 2 trials, 537 in the Phase 2a trial, and over 64,673 in the Phase 3 trials. Additionally, 16,142 subjects were exposed to Ad26.COV.S in the pre-approval access programmes, and 751,922 in the other studies (see Section 5.1, Cumulative Subject Exposure in Clinical Trials).

Cumulative and Interval Patient Exposure from Marketing Experience

Cumulative

A total of 490,569,100 distributed and 52,684,577 administered doses of Ad26.COV2.S vaccine were distributed worldwide from launch to 31 August 2022.

A total of 2,979,798 subjects were administered the homologous Ad26.COV2.S vaccine booster dose in South Africa, South Korea, and the United States (US) from launch to 31 August 2022.

Interval

A total of 128,582,300 distributed and 970,498 administered doses of Ad26.COV2.S vaccine were distributed worldwide from 01 March 2022 to 31 August 2022.

A total of 234,492 subjects were administered the homologous Ad26.COV2.S vaccine booster dose in South Africa, South Korea, and the US from 01 March 2022 to 31 August 2022 (see Section 5.2, Cumulative and Interval Patient Exposure From Marketing Experience).

Summary of the Overall Benefit-Risk Analysis Evaluation

Despite increasing numbers of vaccinated subjects, the ongoing SARS-CoV-2 pandemic remains a public health issue of international concern. The emergence of new virulent lineages has fuelled the need for highly effective preventive measures. Effective and safe COVID-19 vaccines remain a pivotal tool for controlling the disease.

Ad26.COV2.S demonstrated high efficacy against severe/critical disease caused by SARS-CoV2 and protection against hospitalisation and death in clinical trial settings. Analysis of spontaneous reports of vaccination failure did not show trends for lack of efficacy. Altogether, the totality of data demonstrates that vaccination with Ad26.COV2.S remains efficacious against severe/critical COVID-19, including hospitalisations and deaths related to COVID-19, including against some emerging variants. Data on booster usage (homologous or heterologous) continues to demonstrate a favourable benefit-risk profile for a Ad26.COV2.S booster dose at least 2 months and up to 6 months post-primary single dose Ad26.COV2.S administration, to augment protection against COVID-19.

As of 31 August 2022, over 52,684,577 doses of the Ad26.COV2.S vaccine have been administered (CDC 2022, ECDC 2022a, KDCA 2022). Increasing experience based on spontaneous/solicited post-marketing reporting of adverse events, have led to the identification of serious adverse events/reactions such as Thrombosis with Thrombocytopenia Syndrome, Guillain-Barre Syndrome, and immune thrombocytopenia. These risks occur very infrequently, are adequately monitored, and do not outweigh the significant benefits of vaccination with Ad26.COV2.S in controlling the global pandemic. Potential safety concerns will continue to be monitored.

Taking into account the safety data cumulatively, the overall benefit-risk assessment remains favourable for Ad26.COV2.S when used as recommended in the currently approved indications for both primary and booster active immunisation to prevent COVID-19 infection caused by SARS-COV-2 virus in adults ≥18 years of age (see Section 18.2, Benefit-Risk Analysis Evaluation).

Actions Taken and Proposed for Safety Reasons

During this reporting period, several actions were taken for safety reasons in various regions. Details on the actions can be found in Section 3, Actions Taken in the Reporting Interval for Safety Reasons.

Conclusions

During this reporting period, facial paralysis (including Bell's Palsy) and venous thromboembolism were added to the CCDS as post-marketing adverse drug reactions. These new adverse drug reactions do not change the established positive benefit/risk profile of Ad26.COV2.S. Ad26.COV2.S continues to have a favourable benefit-risk profile when used as recommended in the currently approved indications. The Company will continue to monitor potential safety concerns in association with the use of Ad26.COV2.S. Continuous Company safety monitoring will ensure that up to date safety information is available (see Section 19, Conclusions and Actions).

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ACRONYMS/ABBREVIATIONS AND DEFINITIONS OF TERMS

Acronyms/Abbreviations

ADR	Adverse Drug Reaction
Ad26.COV2.S	Adenovirus type 26 Coronavirus 2 Spike
ADEM	Acute Disseminated Encephalomyelitis and Meningoencephalitis
AE	Adverse Event
AEFI	Adverse Event Following Immunisation
AESI	Adverse Event Of Special Interest
AMI	Acute Myocardial Infarction
AR	Adverse reaction
ARDS	Acute Respiratory Distress Syndrome
AST	Aspartate Aminotransferase
ASH	American Society of Hematology
BC	Brighton Collaboration
CAD	Coronary Artery Disease
CCDS	Company Core Data Sheet
CCSI	Company Core Safety Information
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
CIOMS	Council for International Organisation of Medical Sciences
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Coronavirus Disease-2019
cRMP	Core Risk Management Plan
CSR	Clinical Study Report
CT	Clinical Trials
CVST	Cerebral Venous Sinus Thrombosis
CVT	Cerebral Venous Thrombosis
DHPC	Direct Healthcare Professional Communications
DIC	Disseminated Intravascular Coagulation
DLD/DLP	Data Lock Date (used for the ease of reading/ understanding – synonymous with Data Lock Point)
DNA	Deoxyribonucleic Acid
DVT	Deep Vein Thrombosis
ECDC	European Centre for Disease Prevention and Control
EEA	European Economic Area
EMA	European Medicines Agency
EMS	Epidemiologisches Meldesystem
EOI	Event(s) of Interest
FDA	Food and Drug Administration (United States)
FAR	Final Assessment Report
FAS	Final Analyses Set
FOIA	Freedom of Information Act
GBS	Guillain-Barré Syndrome
GVP	Good Pharmacovigilance Practices
HCW	Healthcare Workers
HIV	Human Immunodeficiency Virus
HLT	High Level Term
IBD	International Birth Date
IC	Information Component
ICH	International Council on Harmonisation

ICSR	Individual Case Safety Report
IgAN	Immunoglobulin A Nephropathy
IM	Intramuscular
KDCA	Korea Disease Control and Prevention Agency
LEG	Legally Binding Measure
LL	Line Listing
LOE	Lack Of Efficacy/Effectiveness
MAH	Marketing Authorisation Holder (Company)
MedDRA	Medical Dictionary for Regulatory Activities
MERS-CoV	Middle East Respiratory Syndrome Related Coronavirus
MI	Myocardial Infarction
MOA	Mechanism of Action
mRNA	Messenger Ribonucleic Acid
NA	Neuralgic Amyotrophy
NHP	Nonhuman Primate
O/E	Observed versus Expected
OLL	Oral Lichenoid Lesions
OLP	Oral Lichen Planus
PBRER	Periodic Benefit Risk Evaluation Report
PCR	Polymerase Chain Reaction
PI	Prescribing Information
PM	Product Monograph
PP	Pharmacovigilance Plan
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Reports
PT	Preferred Term (MedDRA)
PV	Pharmacovigilance
PVP	Pharmacovigilance Plan
qBRA	Quantitative Benefit Risk Assessment
RMP	Risk Management Plan
ROR	Reporting Odds Ratio
RR	Reporting Rate
RSI	Reference Safety Information
RSV	Respiratory Syncytial Virus
RWD/RWE	Real World Data and Real World Evidence are synonymous
RWDA	Real World Data Analysis
SAE	Serious Adverse Event
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SCAR	Severe Cutaneous Adverse Reactions
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SOC	System Organ Class (MedDRA)
SSR	Summary Safety Report
STS	Signal Tracking System
TGA	Transient Global Amnesia
TST	Transverse Sinus Thrombosis
TTO	Time To Onset
TTS	Thrombosis with Thrombocytopenia Syndrome
UK	United Kingdom
UMC	Uppsala Monitoring Centre
US	United States (of America)

VAED	Vaccine-associated Enhanced Disease
VAERD	Vaccine Associated Enhanced Respiratory Disease
VAERS	Vaccine Adverse Event Reporting System
VE	Vaccine Efficacy
VITT	Vaccine-induced Immune Thrombotic Thrombocytopenia
VOC	Variants of Concern
VOI	Variants of Interest
VTE	Venous Thromboembolism
vp	Virus particles
WHO	World Health Organisation

Definitions of Terms

Authorised product	A health authority has granted marketing authorisation for the active substance/ product and the licence is currently active. This may not include countries/territories where the product is available via other means (eg, parallel import, or where the health authority does not have a formal authorisation procedure).
Completed clinical trial	A completed clinical trial is defined as having a final Clinical Study Report (CSR) available at the time of data lock for this PBRER reporting period.
Developmental International Birth Date	The date of first approval (or authorisation) to conduct an interventional clinical trial in any country/territory.
Follow-up case	A case for which additional information was received in the period covered by this PBRER.
International Birth Date	The date of first marketing authorisation for any product containing the active substance granted to any company in any country/territory in the world.
Interventional	Clinical trials that may involve the following elements: • Those that involve the use of a medicinal product outside of the terms of the marketing authorisation (eg, new indications, dosage range, frequency, combinations). • Those that influence the freedom of choice for a specific treatment option by the treating health professional (eg, the assignment of a patient to a particular treatment strategy is decided in advance by the protocol). • Those that clearly involve additional diagnostic and/or monitoring procedures that are not part of routine clinical practice.
Latency	Unless otherwise defined, latency is the time from initiation of therapy to onset of adverse event.
Marketing Authorisation Holder (Company)	The generic term "Company-sponsored study" is used throughout the document in lieu of the term "MAH-sponsored study" as the J&J entity acting as study sponsor or as MAH may be different. The term "MAH-sponsored study" is retained for the appendices to keep the terminology in line with the GVP module VII titles for appendices.
Noninterventional	A study where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorisation. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for analysis of collected data.
Ongoing clinical trial	An ongoing clinical trial is defined as a trial in which the first Informed Consent Form has been signed, but does not have a final CSR available at the time of data lock for this PBRER reporting period, regardless of whether the last patient last visit has occurred.

Post Authorisation Safety Study (PASS)	A project, whether interventional or noninterventional, involving an authorised Janssen/Johnson & Johnson medicinal product in an approved indication and includes any of the following as a primary objective: • To quantify potential or identified risks, eg, to characterise the incidence rate, estimate the rate ratio or rate difference in comparison to a nonexposed population or a population exposed to another medicinal product or class of medicinal products as appropriate, and investigate risk factors, including effect modifiers; • To evaluate risks of a medicinal product used in patient populations for which safety information is limited or missing (eg, pregnant women, specific age groups, patients with renal or hepatic impairment or other relevant comorbidity or co-medication); • To evaluate the risks of a medicinal product after long-term use; • To provide evidence about the absence of risks; • To assess patterns of drug utilisation that add knowledge on the safety of the medicinal product or the effectiveness of a risk management measure (eg, collection of information on indication, off label use, dosage, co-medication or medication errors in clinical practice that may influence safety, as well as studies that provide an estimate of the public health impact of any safety concern); • To measure the effectiveness of risk minimisation measures. Note: such guidance does not apply to the measurement of simple process markers (eg, distribution of the tools reaching the target population, assessing clinical knowledge, assessing clinical actions), refer to Guideline on Good Pharmacovigilance Practices (GVP) Module XVI-Guideline on risk minimisation measures: selection of tools and effectiveness indicators.
Source	Classification of reporter or case (eg, health care professional, consumer, literature, study).

1. INTRODUCTION

This Periodic Benefit Risk Evaluation Report (PBRER) for JNJ-78436735 (Ad26.COV2.S), herein referred to as Ad26.COV2.S, summarises the safety data obtained by the Company from worldwide sources for the reporting period of 25 February 2022 to 24 August 2022. The content and format of this report follow the International Council for Harmonisation (ICH) E2C guidelines on the PBRER and Module VII - Periodic Safety Update Reports (PSUR) of the European Medicines Agency (EMA) Guideline on Good Pharmacovigilance Practices (GVP), guidance from the EMA on the Consideration on Core Requirements for PSURs of coronavirus disease-2019 (COVID-19) vaccines,[3] and guidance outlined in EMA's Consideration on Core Requirements for Risk Management Plan (RMP) of COVID-19 vaccine.[4] The International Birth Date (IBD) of Ad26.COV2.S is based on the first regulatory approval in Bahrain on 25 February 2021.

Ad26.COV2.S is indicated for active immunisation for the prevention of COVID-19 in adults greater than or equal to 18 years of age. Ad26.COV2.S is administered as a colourless to slightly yellow, clear to very opalescent single dose suspension, for intramuscular (IM) injection. A booster dose (second dose) may be administered as a homologous booster dose intramuscularly at least 2 months after the primary vaccination in individuals 18 years of age and older. A booster dose may also be administered as a heterologous booster following the completion of a primary messenger ribonucleic COVID-19 vaccination, an adenoviral vector-based COVID-19 vaccine or an inactivated whole-virion COVID-19 vaccine. The dosing interval for the heterologous booster dose is the same as the dosing interval authorised for the booster dose of the vaccine administer for primary vaccination. The indication is as listed in the Company Core Data Sheet (CCDS) and represents the broadest Company-supported use.

Ad26.COV2.S is a monovalent vaccine composed of a recombinant, replication-incompetent human adenovirus type 26 (Ad26) vector, constructed to encode the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) spike (S) protein. Following vaccination, the S protein is expressed and stimulates an immune response. One dose of Ad26.COV2.S contains $5x10^{10}$ virus particles (vp) in 0.5 mL. Ad26.COV2.S is produced in the PER.C6® TetR Cell Line and by recombinant deoxyribonucleic acid (DNA) technology. Ad26.COV2.S contains genetically modified organisms. Information regarding the pharmacodynamic and pharmacokinetic properties is contained in the appended CCDS.

Ad26.COV2.S contains the following excipients: citric acid monohydrate, trisodium citrate dihydrate, ethanol, 2-hydroxypropyl-β-cyclodextrin, polysorbate-80, sodium chloride, sodium hydroxide, hydrochloric acid, and water for injections.

[3] EMA/362988/2021 (dated 08 July 2021)

[4] EMA/PRAC/709308/2022 (dated 1 September 2022)

2. WORLDWIDE MARKETING AUTHORISATION STATUS

The IBD for Ad26.COV2.S is 25 February 2021 based on the first authorisation in Bahrain. The indications and the approved dose can be found in Section 1, Introduction.

Ad26.COV2.S is authorised in 108 countries/territories and import licences have been granted in 20 countries/territories worldwide (see Table 1 and Table 2). In addition, Ad26.COV2.S obtained an Emergency Use Listing by the World Health Organization (WHO).

Table 1: List of Countries/Territories Where Ad26.COV2.S is Authorised (n=108)

Algeria	Czech Republic	Kuwait	Qatar
Antigua and Barbuda	Denmark	Laos	Romania
Argentina	Egypt	Latvia	Rwanda
Australia	Estonia	Lebanon	Saudi Arabia
Austria	Ethiopia	Lichtenstein	Sierra Leone
Bahamas	Finland	Lithuania	Slovakia
Bahrain	France	Luxembourg	Slovenia
Bangladesh	Gabon	Madagascar	Solomon Island
Belgium	Gambia	Malaysia	Somalia
Belize	Georgia	Malta	South Africa
Bolivia	Germany	Mauritius	South Sudan
Botswana	Ghana	Mexico	Spain
Brazil	Greece	Moldova	Sudan
Bulgaria	Guatemala	Mozambique	Sweden
Burundi	Guinea	Nepal	Switzerland
Cabo Verde	Guyana	Netherlands	Syria
Cameroon	Haiti	New Zealand	Thailand
Canada	Hungary	Nicaragua	Trinidad and Tobago
Central African Republic	Iceland	Nigeria	Tunisia
Chad	India	Norway	Uganda
Chile	Indonesia	Oman	Ukraine
Colombia	Ireland	Panama	United Arab Emirates
Comoros	Italy	Papua New Guinea	United Kingdom (Great Britain)
Congo	Jamaica	Peru	United States
Cote d'Ivoire	Japan	Philippines	Vanuatu
Croatia	Kenya	Poland	Vietnam
Cyprus	Korea	Portugal	Zimbabwe

Key: n=Number

Table 2: List of Countries/Territories Where Ad26.COV2.S is Granted Import Licences (n=20)

Angola	Eswatini	Malawi	Sao Tome and Principe
Benin	Guinea-Bissau	Mali	Senegal
Burkina Faso	Lesotho	Mauritania	Tanzania
Congo (Democratic Republic of)	Liberia	Namibia	Togo
Djibouti	Libya	Niger	Zambia

Key: n=Number

3. ACTIONS TAKEN IN THE REPORTING INTERVAL FOR SAFETY REASONS

The significant actions taken for safety reasons during the period covered by this report are presented below in Table 3.

Table 3: Significant Actions Taken for Safety Reasons During the Reporting Period

Date	Country/Territory	Issue	Action Taken
29 March 2022	EU	Completion of an additional pharmacovigilance activity mentioned in the EU RMP version 3.1 (approved on 13 January 2022 via procedure: EMEA/H/C/005737/II/0029).	On 29 March 2022, a grouping of Type II-variations (EMA/H/C/5737/II/0047/G) covering the final study reports of 5 non-clinical TTS characterisation studies regarding Ad26.COV2.S was submitted.
30 March 2022	EU	Completion of an additional pharmacovigilance activity mentioned in the EU RMP version 3.1 (approved on 13 January 2022 via procedure: EMEA/H/C/005737/II/0029).	On 30 March 2022, a grouping of Type II-variations (EMA/H/C/5737/II/0048/G) covering the final study reports of 4 clinical TTS characterisation studies regarding Ad26.COV2.S and an updated EU RMP (version 4.1) was submitted to EMA.
12 April 2022	EU	Request in final PRAC outcome for the SSR(EMEA/H/C/005737/MEA/014.8) covering 01 November 2021 to 15 January 2022 to include cutaneous small vessel vasculitis as an ADR in the EUPI	PRAC request to include small vessel vasculitis with cutaneous manifestations as an ADR in the EUPI. EMA proposed to change the wording to "cutaneous small vessel vasculitis" in an email dated 15 March 2022. Type IB variation submitted to EMA on 12 April 2022. Notification is received on 19 April 2022 (EMA/H/C/5737/IB/0051). Submissions to other HA's were made in line with local requirements.
05 May 2022	EU	A pooled analysis of the double-blind phase of 5 clinical trials conducted by the MAH at the time of the preparation of the PBRER (period: 25 August 2021 to 24 February 2022), showed a numerical imbalance between Ad26.COV2.S vaccine and placebo for facial paralysis/Bell's palsy. A cumulative assessment of available safety data has been carried out as a result of this imbalance and is presented in the PBRER with the reporting period of 25 August 2021 to 24 February 2022. Based on the totality of the data, the MAH has concluded there is a reasonable possibility of a causal association between Ad26.COV2.S vaccine and facial paralysis/Bell's palsy.	The product information was amended to include facial paralysis (including Bell's palsy) as an adverse reaction and was included in the PBRER submission (EMEA/H/C/PSUSA/00010916/202202) performed on 05 May 2022.

Table 3: Significant Actions Taken for Safety Reasons During the Reporting Period

Date	Country/Territory	Issue	Action Taken
05 May 2022	US	EUA fact sheet updates for prominent placement for TTS warning and limitation of use of Ad26.COV2.S vaccine.	FDA reached out to Janssen on 27 April 2022 with proposed updates to the HCP and RCG fact sheets. The final documents were submitted to the EUA, which implemented the placement of warning for TTS at the beginning of the HCP fact sheet and limitation of use. RCG fact sheet was updated in accordance. FDA provided approval in form of updated LoA for the EUA on the same date. HA submissions in other countries/territories were made in line with local requirements. The Company did not consider this an ESI.
09 May 2022	TUN	Suspension of the use of "Johnson & Johnson" COVID-19 vaccine by the Health authority.	Provisional suspension, by precautionary measure, the use of the specialty Ad26.COV2.S vaccine given the occurrence of adverse effects and following the latest US FDA recommendation to limit the use of the "Johnson & Johnson" coronavirus vaccine. The Exceptional Marketing Authorisation previously issued is not suspended.
20 June 2022	Japan	Externally identified SSI.	PMDA requested that "immune mediated and neuroinflammatory events" are included as an important potential risk in the J-RMP. Consequently, a precaution statement is included in the initial Japan PI, approved by the MHLW on 20 June 2022, as a risk minimisation measure for this J-RMP important potential risk. HA notifications in other countries/territories were made in line with local requirements. The Company did not consider this an ESI.
30 June 2022	EU	A pooled analyses of safety data from Phase 1, 2 and 3 clinical studies with Ad26.COV2.S to assess the reactogenicity profile and the frequency of adverse events after primary vaccination with Ad26.COV2.S and after homologous boosting with Ad26.COV2.S in adults aged ≥18 years is submitted to EMA as a Type II variation.	The product information was amended (EMEA/H/C/005737/II/0060) in accordance with the results obtained from pooled analyses of safety data.

Table 3: Significant Actions Taken for Safety Reasons During the Reporting Period

Date	Country/Territory	Issue	Action Taken
07 July 2022	Jordan	EUA not renewed.	Emergent as API manufacturer for Ad26.COV2.S is currently not considered to be compliant with GMP for the manufacture of this API.

Key: ADR=Adverse Drug Reaction; API=Active Pharmaceutical Ingredient; AMI=Acute Myocardial Infarction; AR=Aggregate Report; CAD=Coronary Artery Disease; COVID-19=Coronavirus Disease-2019; EMA=European Medicines Agency; EMEA=European Medicines Evaluation Agency; ESI=Emerging Safety Issue; EU=European Union; EUA=Emergency Use Authorisation; EUPI=European Union Product Information; FDA= Food and Drug Administration; GMP=Good Manufacturing Practice; HA=Health Authority; HC=Health Canada; HCP=Health Care Professional; J-RMP=Japan-Risk Management Plan; LoA=Letter of Acceptance; MAH=Marketing Authorisation Holder; MHLW=Ministry of Health, Labour and Welfare; MI=Myocardial Infarction; O/E=Observed versus Expected; PBRER= Periodic Benefit-Risk Evaluation Report; PI=Package Insert; PM=Product Monograph; PMDA=Pharmaceuticals and Medical Devices Agency; PRAC=Pharmacovigilance Risk Assessment Committee; RCG=Recipients and Caregivers; RMP=Risk Management Plan; SSI=Significant Safety Issue; SSR=Summary Safety Report; TTS=Thrombosis With Thrombocytopenia Syndrome; US=United States; NZ=New Zealand

4. 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 June 2022. Significant changes to the CCDS (ie, CCSI) made within the reporting interval are listed in Table 4.

Table 4: Significant Changes to the Ad26.COV2.S CCDS During the Reporting Period

CCDS Version and Date	CCDS Section	Description of Change(s)
CCDS V12 Version Date: 14 June 2022	Dosage and Administration, Adverse Reactions, Clinical Studies.	The CCDS has been revised to include information from COV2008, COVBOOST, and MIXNMatch studies to support the booster dose as follows: -support 6-month dosing interval for the homologous booster dose (COV2008); -additional information from COV2008, COVBOOST and MIXNMatch studies to support heterologous booster following primary vaccination with an mRNA COVID-19 vaccine; -additional safety information related to an increased trend in reactogenicity seen after a heterologous booster dose with an mRNA COVID-19 vaccine; -inclusion of information in relation to booster dose after AstraZeneca COVID-19 vaccine (COVBOOST); -inclusion of information in relation to booster dose after CoronaVac (RHH-001 Study).
CCDS V13 Version Date: 28 June 2022	Adverse Reactions	Safety pooling for the primary vaccination Addition of Facial paralysis (including Bell's palsy) as a post-marketing adverse reaction. Addition of Venous thromboembolism as a post-marketing adverse reaction.

Key: CCDS=Company Core Data Sheet; COVID-19=Coronavirus Disease-2019; mRNA=Messenger Ribonucleic Acid; V=Version

Please see Appendix 1 for the version of the CCDS in effect at the end of the reporting period.

5. ESTIMATED EXPOSURE AND USE PATTERNS

5.1. Cumulative Subject Exposure in Clinical Trials

Overall, an estimated 82,152 healthy subjects have been enroled in the Ad26.COV.S clinical programme, of which approximately 68,611 subjects have received Ad26.COV.S in the Company-sponsored interventional clinical trials (see Table 5). Of these, 580 subjects were

exposed to Ad26.COV.S in the Phase 1 trials,[5] 935 in a Phase 1/2a trial,[6] 1,886 in the Phase 2 trials,[7] 537 in the Phase 2a trial,[8] and over 64,673 in the Phase 3 trials.[9]

Additionally, 16,142 subjects were exposed to Ad26.COV.S in the pre-approval access programmes,[10] and 751,922 in the other studies.[11]

Table 5: Estimated Cumulative Subject Exposure From Clinical Trials

Treatment	Number of Subjects
Ad26.COV2.S	68,611
Comparator	N/A
Placebo	39,370

Note: Number of subjects exposed to at least 1 study vaccine, recorded in the study databases up to cut-off date (24 August 2022).
Trials included: VAC31518COV1001, VAC31518COV1002, VAC31518COV1003, VAC31518COV2001, VAC31518COV2004, VAC31518COV2008, VAC31518COV3001, VAC31518COV3003, VAC31518COV3005, VAC31518COV3006 and VAC31518COV3009.
The number of subjects exposed to study vaccine in blinded trials (Ad26 and placebo for Trial VAC31518COV3005, and placebo for Trial VAC31518COV3006) are estimates.
A total of 25,829 subjects (506 from Trial VAC31518COV1001, 150 from Trial VAC31518COV2001, 16,045 from Trial VAC31518COV3001, 781 from Trial VAC31518COV3005, 114 from Trial VAC31518COV3006, 8,233 from Trial VAC31518COV3009) that received a regimen with both Ad26.COV2.S and placebo, subjects are counted for both Ad26.COV2.S and placebo.

Table 6 and Table 7 show cumulative subject exposure by age and sex, and by race from completed clinical trial, respectively.

Table 6: Cumulative Subject Exposure to Ad26.COV2.S From Completed Clinical Trial by Age and Sex

Age Range (Years)[a]	Number of Subjects		
	Male	Female	Total
12 to 17	10	20	30
18 to 40	129	60	189
41 to 64	87	51	138
65 to 75	92	61	153
>75	21	6	27
Total	**339**	**198**	**537**

[5] Trials included: VAC31518COV1002, and VAC31518COV1003.

[6] Trial included: VAC31518COV1001.

[7] Trials included: VAC31518COV2004, VAC31518COV2008, and VAC31518COV3006.

[8] Trial included: VAC31518COV2001.

[9] Trials included: VAC31518COV3001, VAC31518COV3003, VAC31518COV3005, and VAC31518COV3009.

[10] Programmes included: VAC31518COV4006 and VAC31518COV4007.

[11] Studies included: COV-BOOST (VAC31518COV2009), VAC31518COV2012, VAC31518COV2016 (AUR1-8-341), VAC31518COV3012 (Sisonke [Together]), VAC31518COV3018, VAC31518COV3021 (Sisonke Boost Open-label Study [SISONKE2]), VAC31518COV4012, and DMID 21-0012.

Table 6: Cumulative Subject Exposure to Ad26.COV2.S From Completed Clinical Trial by Age and Sex

Age Range (Years)[a]	Number of Subjects		
	Male	Female	Total

Note: Trial included: VAC31518COV2001.
a: Data from completed trials as of 24 August 2022.

Table 7: Cumulative Subject Exposure to Ad26.COV2.S From Completed Clinical Trial by Race/Ethnic Group

Race/Ethnic Group[a]	Number of Subjects
American Indian or Alaska Native	2
Asian	5
Black or African American	3
Native Hawaiian or other Pacific Islander	0
White	520
Multiple	1
Unknown	4
Not reported	2
Total	**537**

Note: Trial included: VAC31518COV2001.
a: Data from completed studies as of 24 August 2022.

5.2. Cumulative and Interval Patient Exposure From Marketing Experience

Post-approval (non-clinical trial) 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 2022) for the United States (US), European Centre for Disease Prevention and Control (ECDC 2022) for European Economic Area (EEA) countries/territories, Korea Disease Control and Prevention Agency (KDCA 2022) for South Korea, Ministério da Saúde (Ministério da Saúde 2021) for Brazil, and National Department of Health (NDH 2022) for South Africa.

The vaccine exposure figures described in this section are an overall estimation with some uncertainties regarding the lack of exposure information received from many countries/territories.

Interval Exposure Estimates

The interval subject exposure for the Ad26.COV2.S vaccine during the reporting period (01 March 2022 to 31 August 2022) is provided in Table 8.

Table 8: Subject Exposure to the Ad26.COV2.S Vaccine During the Reporting Period (01 March 2022 to 31 August 2022)

Region/Country/Territory	Number of Distributed Doses[a]	Number of Administered Doses[b]
EEA		
Austria	0	5,326
Belgium	0	2,848
Bulgaria	0	18,340
Croatia	31,200	4,538
Cyprus	16,800	1,401
Czechia	55,200	1,890

Table 8: Subject Exposure to the Ad26.COV2.S Vaccine During the Reporting Period (01 March 2022 to 31 August 2022)

Region/Country/Territory	Number of Distributed Doses[a]	Number of Administered Doses[b]
Estonia	0	1,225
France	0	19,677
Germany	1,000,800	128,246
Greece	0	54,912
Hungary	369,600	10,300
Iceland	0	20
Italy	0	249
Latvia	0	1,852
Liechtenstein	NR	3
Lithuania	50,400	1,484
Luxembourg	0	36
Malta	0	116
Norway	0	313
Poland	0	161,697
Portugal	0	4,163
Romania	0	28,117
Slovakia	0	2,479
Spain	0	281
ROW		
Afghanistan	8,150,400	NR
Benin	885,600	NR
Brazil	500	NR
Burkina Faso	2,007,650	NR
Cameroon	2,340,000	NR
Chad	6,982,550	NR
Colombia	4,800	NR
Congo (Brazzaville)	1,177,400	NR
Congo (Kinshasa)	6,213,600	NR
Djibouti	158,400	NR
Ethiopia	14,817,600	NR
Gambia	192,000	NR
Guinea	172,800	NR
Guinea-Bissau	237,600	NR
Guyana	36,000	NR
Kenya	4,327,200	NR
Liberia	1,944,000	NR
Madagascar	1,718,400	NR
Malawi	1,987,200	NR
Mali	907,200	NR
Namibia	151,200	NR
Niger	561,600	NR
Nigeria	36,086,400	NR
Papua New Guinea	216,000	NR
Sierra Leone	1,776,000	NR
Solomon Islands	100,800	NR
South Africa	NR	84,146
South Korea	491,600	722
South Sudan	1,891,300	NR
Sudan	2,829,600	NR
Uganda	3,784,800	NR
Ukraine	100,800	NR
United Republic of Tanzania	13,372,250	NR

Table 8: Subject Exposure to the Ad26.COV2.S Vaccine During the Reporting Period (01 March 2022 to 31 August 2022)

Region/Country/Territory	Number of Distributed Doses[a]	Number of Administered Doses[b]
Vanuatu	14,400	NR
Yemen	237,600	NR
Zambia	5,219,950	NR
US	**5,963,100**	**436,117**
Total	**128,582,300**	**970,498**

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; NDH=National Department of Health; NR=Not Reported; ROW=Rest of World; US=United States

a: Number of vaccine doses distributed were reported from LYNX Finance.

b: Number of vaccine doses administered were reported from CDC for the US, from ECDC for EEA countries/territories, KDCA for South Korea, and NDH for South Africa. The data for administered doses for South Africa were available from 30 June 2022 to 31 August 2022.

A total of 128,582,300 doses[12] of Ad26.COV2.S vaccine were distributed worldwide from 01 March 2022 to 31 August 2022.

A total of 970,498 doses[12] of Ad26.COV2.S vaccine were administered worldwide from 01 March 2022 to 31 August 2022.

Cumulative Exposure Estimates

The cumulative subject exposure for the Ad26.COV2.S vaccine from launch to 31 August 2022 is provided in Table 9.

Table 9: Cumulative Subject Exposure to the Ad26.COV2.S Vaccine From Launch to 31 August 2022

Region/Country/Territory	Number of Distributed Doses[a]	Number of Administered Doses[b]
EEA		
Austria	1,292,400	367,950
Belgium	629,200	427,716
Bulgaria	1,777,300	526,264
Croatia	309,550	204,108
Cyprus	142,500	30,944
Czechia	547,200	412,908
Denmark[c]	1,198,800	46,626
Estonia	110,800	78,932
Finland	68,400	NR
France	3,416,300	1,088,828
Germany	7,818,150	3,749,759
Greece	1,521,600	783,384
Hungary	4,309,200	341,801
Iceland[d]	33,500	54,303
Ireland[c]	281,500	237,097

[12] There has been a decrease in both the number of distributed and administered doses due to a decrease in demand for the vaccine in both the US and other countries/territories.

Table 9: Cumulative Subject Exposure to the Ad26.COV2.S Vaccine From Launch to 31 August 2022

Region/Country/Territory	Number of Distributed Doses[a]	Number of Administered Doses[b]
Italy	2,370,000	1,482,636
Latvia	767,800	277,651
Liechtenstein	NR	264
Lithuania[d]	287,200	295,758
Luxembourg	80,200	41,521
Malta	116,400	32,398
Netherlands[c]	2,464,800	755,619
Norway	403,900	7,325
Poland	15,523,300	2,916,681
Portugal[d]	993,600	1,136,990
Romania	4,080,300	2,064,966
Slovakia	475,200	185,185
Slovenia[c]	230,400	135,989
Spain	2,659,000	1,980,822
Sweden	55,200	NR
ROW		
Afghanistan	14,695,250	NR
Algeria	6,285,600	NR
Angola	4,696,050	NR
Antigua and Barbuda	38,400	NR
Bahamas	38,400	NR
Bangladesh	679,750	NR
Belize	148,800	NR
Benin	3,566,400	NR
Bolivia	1,008,000	NR
Botswana	1,346,400	NR
Brazil	41,000,500	4,821,930
Burkina Faso	4,057,250	NR
Burundi	302,400	NR
Cambodia	1,060,100	NR
Cameroon	3,742,250	NR
Canada	168,000	NR
Central African Republic	2,016,300	NR
Chad	7,793,650	NR
Colombia	11,504,800	NR
Congo, (Brazzaville)	2,696,600	NR
Congo, (Kinshasa)	8,632,800	NR
Côte D'ivoire	5,272,600	NR
Djibouti	360,000	NR
Egypt	15,513,450	NR
Ethiopia	41,759,750	NR
Gabon	866,400	NR
Gambia	547,200	NR
Ghana	8,788,800	NR
Guinea	1,080,000	NR
Guinea-Bissau	1,368,000	NR
Guyana	96,000	NR
Haiti	165,600	NR
Jamaica	216,000	NR
Kenya	14,745,050	NR
Lao PDR	1,771,200	NR
Lebanon	336,000	NR

Table 9: Cumulative Subject Exposure to the Ad26.COV2.S Vaccine From Launch to 31 August 2022

Region/Country/Territory	Number of Distributed Doses[a]	Number of Administered Doses[b]
Lesotho	1,033,050	NR
Liberia	3,132,000	NR
Madagascar	3,537,950	NR
Malawi	3,568,350	NR
Mali	1,452,000	NR
Mauritania	2,282,400	NR
Mauritius	439,200	NR
Mexico	1,350,000	NR
Moldova	302,400	NR
Morocco	302,400	NR
Mozambique	8,989,700	NR
Namibia	650,400	NR
Nepal	3,711,500	NR
Nicaragua	993,600	NR
Niger	3,470,400	NR
Nigeria	49,002,850	NR
Papua New Guinea	820,800	NR
Philippines	12,725,650	NR
Rwanda	897,600	NR
Saint Lucia	7,200	NR
Sao Tome and Principe	100,800	NR
Senegal	1,739,100	NR
Sierra Leone	2,877,600	NR
Solomon Islands	100,800	NR
South Africa	19,623,200	7,805,749
South Korea	3,411,000	1,517,251
South Sudan	2,793,050	NR
Sudan	6,728,300	NR
Swaziland	302,400	NR
Switzerland	200	NR
Syrian Arab Republic (Syria)	3,458,400	NR
Togo	2,620,800	NR
Trinidad and Tobago	259,200	NR
Tunisia	1,540,800	NR
Turkey	832,800	NR
Uganda	15,820,800	NR
Ukraine	100,800	NR
United Republic of Tanzania	14,953,400	NR
Vanuatu	43,150	NR
Yemen	1,197,600	NR
Zambia	9,842,350	NR
US	41,225,650	18,875,222
Total	**490,569,100[e]**	**52,684,577**

Key: CDC=Centers for Disease Control and Prevention, ECDC=European Centre for Disease Prevention and Control, EEA=European Economic Area; EU=European Union; KDCA=Korea Disease Control and Prevention Agency; NDH=National Department of Health; NR=Not Reported; PDR=People's Democratic Republic; ROW=Rest of World; US=United States

a: Number of vaccine doses distributed were reported from LYNX Finance.

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

Table 9: Cumulative Subject Exposure to the Ad26.COV2.S Vaccine From Launch to 31 August 2022

Region/Country/Territory	Number of Distributed Doses[a]	Number of Administered Doses[b]

from NDH for South Africa. The data for administered doses for Brazil were last updated by the Ministério da Saúde website on 15 November 2021.

c: Information within the ECDC website states that, "*All data are subject to retrospective correction*" which may be a reason a decrease in the cumulative exposure has been observed for this country/territory. Exposure values were obtained from the most current counts as of 31 August 2022.

d: The number of distributed doses is less than the number of administered doses. This is the limitation when the data was distributed and reported. Some countries/territories may donate their surplus to other countries/territories resulting in this difference.

e: This count includes donated doses by the US and EU to various countries/territories, including donations through the GAVI/COVAX agreement.

A total of 490,569,100 doses of Ad26.COV2.S vaccine were distributed worldwide from launch to 31 August 2022.

A total of 52,684,577 doses of Ad26.COV2.S vaccine were administered worldwide from launch to 31 August 2022.

Homologous Ad26.COV2.S Vaccine Booster Doses for Interval and Cumulative Period

The list of countries/territories along with number of homologous Ad26.COV2.S vaccine booster doses for the interval and cumulative period is provided in Table 10.

Table 10: Total Number of Subjects With the Homologous Ad26.COV2.S Vaccine Booster Doses

Country/Territory	Interval	Cumulative
South Africa	95,960	1,386,703
South Korea	407	26,986
US	138,125	1,566,109
Total	**234,492**	**2,979,798**

Key: US=United States

A total of 234,492 subjects were administered the homologous Ad26.COV2.S vaccine booster dose in South Africa, South Korea, and the US from 01 March 2022 to 31 August 2022.

A total of 2,979,798 subjects were administered the homologous Ad26.COV2.S vaccine booster dose in South Africa, South Korea, and the US from launch to 31 August 2022.

Exposure by Age for Ad26.COV2.S in EEA

Age stratifications based upon the number of administered doses available for EEA from the ECDC is unavailable as the data were last updated in September 2021. In addition, other stratifications such as sex, usage in pregnant or breastfeeding women, usage in hepatic impairment population, and usage in renal impairment population are also unavailable at this time.

Post-authorisation use in special populations

There is no available information on post-authorisation use of Ad26.COV2.S in special populations.

5.3. Other Post-approval Use

There is no available information on the pattern of use of Ad26.COV2.S which may be considered relevant for the interpretation of safety data.

6. DATA IN SUMMARY TABULATIONS

Database

The Company global safety database contains adverse event (AE) reports received from several sources: spontaneous notification, regulatory authorities, medical literature, clinical trials, post-marketing studies, registries, and other solicited sources.

The Cumulative Summary Tabulations of Serious Adverse Events (SAEs) From Clinical Trials (CT Tabulations) display all serious AEs from clinical trials. The CT Tabulations inclusion criteria was expanded: all clinical trials are in scope (including Company-sponsored and non-Company-sponsored clinical trials). However, protocols which do not report serious AEs are not displayed in the output.

The Cumulative and Interval Summary Tabulations From Post-marketing (PM) Sources inclusion criteria was expanded to include adverse reactions (ARs) from special situation cases (eg, pregnancy, overdose, medication error) with no additional ARs reported. No ARs from any type of studies (ie, clinical trials, noninterventional post-marketing studies and other solicited sources) are reported in the "Spontaneous" column of the PM tabulations.

Nonserious ARs from noninterventional post-marketing studies and other solicited sources are not presented in either of the tabulations.

Interval is defined as all cases received during the reporting period of this PBRER which have been reviewed and assessed. Within this PBRER, the term initial will be used to present all initial cases received. Cumulative is defined as all cases received (initial and follow-ups) from launch to the end date of this PBRER.

Please refer to Sections 6.2 and 6.3 for details regarding content of tabulations in appendices.

Primary Dose versus Booster Dose

Primary dose is defined as the first incidence of administration of the vaccine and booster dose is defined as administration of the vaccine after the primary dose. Although the overall tabulations contain all cases and events (primary dose and booster dose), the searches for each topic were conducted separately based on the configuration outputs. Within this PBRER, primary dose and booster dose subsections are presented separately for each topic. As such, the counts of each subsection are not additive.

6.1. Reference Information

All events are coded using Medical Dictionary for Regulatory Activities (MedDRA), version 25.0. Caution is advised when comparing current data with those of Ad26.COV2.S PBRERs using earlier MedDRA versions/coding dictionaries.

6.2. Cumulative Summary Tabulations of Serious Adverse Events From Clinical Trials

Appendix 2.1.1 and Appendix 2.1.2 contain a cumulative tabulation of SAEs from Company-sponsored and non-Company-sponsored clinical trials, reported from the Developmental International Birth Date to the data lock date (DLD) of this Ad26.COV2.S PBRER (all protocols and by protocol, respectively). SAEs from all clinical trials are included regardless of causality (ie, related and not related SAEs are included). Protocols which do not report SAEs are not displayed in the outputs.

SAEs from blinded and unblinded clinical trial cases are included. Unblinded SAEs might originate from completed trials and individual cases that have been unblinded for safety-related reasons (eg, expedited reporting), if applicable. Data have not been unblinded for the specific purpose of preparing the Ad26.COV2.S PBRER. SAEs are organised by protocol number and then MedDRA System Organ Class (SOC) in international order for the investigational medicinal product, blinded treatment and comparators (active and placebo).

6.3. Cumulative and Interval Summary Tabulations From Post-marketing Sources

Appendix 2.2 contains cumulative and interval summary tabulations of "suspected adverse reactions" (thereafter called "adverse reactions" [ARs])[13] received cumulatively to the DLD of this PBRER. These ARs 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. Appendix 2.2 also displays ARs from special situation cases (eg, pregnancy, off label use, overdose, medication error) with no additional ARs reported.

Data are presented side-by-side and organised by MedDRA SOC and then Preferred Terms (PTs) in international order. An AR received during the current reporting interval is captured in both the Interval and Cumulative columns. The count of ARs received during the interval period comprises all ARs (whether new or not) from both initial and follow-up individual case safety reports (ICSRs). The cumulative count would only increase for unique/new ARs from 1 reporting

[13] As described in ICH-E2D guideline, for marketed medicinal products, spontaneously reported adverse events usually imply at least a suspicion of causality by the reporter and should be considered to be suspected adverse reactions for regulatory reporting purposes.

period to the next. The ARs displayed in the interval period tabulations are not additive to the previous cumulative figure(s).

During the reporting period, 25,785 serious ARs and 42,477 nonserious ARs were received from spontaneous sources, and 658 serious ARs were received from noninterventional post-marketing studies and other solicited sources.[14]

From spontaneous sources, noninterventional post-marketing studies, and other solicited sources, the SOCs including the most reported were:

- General Disorders and Administration Site Conditions (22,636);
- Nervous System Disorders (10,227);
- Musculoskeletal and Connective Tissue Disorders (7,178);
- Infections and Infestations (6,574);
- Gastrointestinal Disorders (3,259)

Cumulatively, 92,932 serious ARs (91,813 spontaneous, 1,119 from noninterventional post-marketing studies and other solicited sources) were received by the Market Authorisation Holder (MAH).

7. SUMMARIES OF SIGNIFICANT FINDINGS FROM CLINICAL TRIALS DURING THE REPORTING INTERVAL

Appendix 4.1 contains a list of Company-sponsored interventional trials with the primary aim of identifying, characterising, or quantifying a safety hazard, confirming the safety profile of the medicinal product, or measuring the effectiveness of risk minimisation measures that were completed or ongoing during the reporting interval.

7.1. Completed Clinical Trials

A "completed clinical trial" is defined as a trial for which a final clinical study report (CSR) is available (ie, CSR completed during the PBRER reporting period).

During the PBRER reporting period, 1 Company-sponsored interventional clinical trial (VAC31518COV2001) of Ad26.COV2.S was completed. The safety summary from this completed clinical trial is presented below.

Trial VAC31518COV2001

This was a Phase 2a, randomised, double-blind, placebo-controlled, multicentre trial evaluating Ad26.COV2.S across a range of dose levels and vaccination intervals in healthy adults aged 18 to 55 years inclusive, and adults in good or stable health aged 65 years and older to evaluate

[14] This does not include interventional clinical trials.

a single-dose level of Ad26.COV2.S (2.5×10^{10} vp) in healthy adolescents aged 16 to 17 years inclusive. In this trial, total 537 participants were exposed to Ad26.COV2.S of which 507 were adults and 30 were adolescents.

Safety Summary

The safety data for adults and adolescents is described below.

Adults

Deaths, Serious Adverse Events, Adverse Events of Special Interest, and Adverse Events Leading to Vaccine Discontinuation

In total, 9 participants (1 in the 1.25×10^{10}, 1.25×10^{10} vp [56-day] group, 1 in the 2.5×10^{10}, 2.5×10^{10} vp [56-day] group, 3 in the 5×10^{10}, 5×10^{10} vp [56-day] group, 1 in the 5×10^{10}, 5×10^{10} vp [84-day] group, 2 in the 5×10^{10} vp, placebo [56-day] group, and 1 in the 1×10^{11} vp, placebo [56-day] group) experienced 1 or more SAEs, each considered unrelated to study vaccine by the corresponding investigator. Six participants each experienced 1 SAE (hepatic cyst, osteoarthritis, cerebrospinal fluid leakage, prostate cancer, death, and adenocarcinoma of colon). Three participants experienced a higher number of individual or distinct SAEs: pyrexia and pancytopenia (n=1); acute myeloid leukaemia, pneumonia, and systemic candida infection (n=1); and lung adenocarcinoma and bacteraemia (n=1). Two participants discontinued study vaccination due to an SAE: lung adenocarcinoma and acute myeloid leukaemia. One participant in the 2.5×10^{10}, 2.5×10^{10} vp (56-day) group died due to an unknown cause. The event was considered to be unrelated to the study vaccine by the investigator.

Two thrombotic events were reported. One participant in the 5×10^{10} vp, placebo (56-day) group had Grade 2 thrombophlebitis at Day 2 (ie, 1 day after the first vaccination) and 1 in the 5×10^{10}, 5×10^{10} vp (56-day) group had Grade 3 ischaemic stroke 8 days post-antigen presentation. None of the thrombotic events occurred concurrently with thrombocytopenia. Two participants in the single-dose regimen groups, 7 in the 2-dose regimen groups, and 3 in the placebo groups experienced AEs leading to vaccine discontinuation of which 1, 5, and 3 participants, respectively, had confirmed COVID-19 infection and discontinued study vaccination per study protocol. Overall, COVID-19 related AEs were reported in 3 participants in the active single-dose regimen groups, 8 in the active 2-dose regimen groups, and 5 in the placebo groups.

Solicited Adverse Events

Solicited Local Adverse Events

Post-dose 1, post-dose 2, and post-antigen presentation, the most frequently reported solicited local AE was vaccination site pain, with a frequency that was higher in participants in the Ad26.COV2.S groups compared to participants in the placebo groups. A trend towards a decrease in the frequency of solicited local AEs with decreasing Ad26.COV2.S dose level was observed in the active vaccine groups post-dose 1. Apart from 2 Grade 3 AEs of vaccination site pain, all other solicited local

AEs were Grade 1 or 2 severity. The frequency of solicited local AEs post-dose 1, post-dose 2, and post-antigen presentation was similar within each of the active 2-dose regimen groups. The frequency and severity of solicited local AEs post-dose 2 were similar for participants in the 56-day and in the 84-day 2-dose regimen groups. For the single-dose regimen groups, the frequency of solicited local AEs was similar post-dose 1 and post-antigen presentation within each of the active single-dose regimen groups and lower post-antigen presentation than post-dose 1. A trend towards a decrease in the frequency and severity of solicited local AEs with increasing age of participants was observed in all active vaccine groups post any Ad26.COV2.S administration.

Solicited Systemic Adverse Events

Post-dose 1, post-dose 2, and post-antigen presentation, the most frequently reported solicited systemic AEs (at least 10% in any active vaccine group) were fatigue, headache, and myalgia, with a frequency that was higher in participants in the Ad26.COV2.S groups post any dose, compared to participants in the placebo groups. Most of the solicited systemic AEs were Grade 1 or 2 severity. Grade 3 solicited systemic AEs in the active vaccine groups were less frequently reported post-dose 2 and post-antigen presentation than post-dose 1. The frequency of solicited systemic AEs post-dose 1 and post-dose 2 was similar within each of the active 2-dose regimen groups; a trend towards a decrease in the frequency and severity of solicited systemic AEs with decreasing Ad26.COV2.S dose level was observed post-dose 1 and 2 in the active 2-dose regimen groups. Frequency and severity of solicited systemic AEs post-dose 2 were similar for participants in the 56-day and in the 84-day 2-dose groups. The frequency of solicited systemic AEs post-antigen presentation was similar for the active 2-dose regimen groups and similar ie, lower than post-dose 1. For the single-dose regimen groups, reactogenicity was increased in the regimen with the highest Ad26.COV2.S dose level and reactogenicity within each single-dose regimen group was less post-antigen presentation versus post-dose 1. In addition, a trend towards a decrease in the frequency and severity of systemic solicited AEs with increasing age of participants was observed in all active vaccine groups post any Ad26.COV2.S administration.

Pyrexia (defined as body temperature ≥38.0°C/100.4°F) was reported less frequently post-dose 2 and post-antigen presentation than post-dose 1 and its reported frequency and severity increased with increasing Ad26.COV2.S dose level. All Grade 3 cases of pyrexia, of which most post 1×10^{11} vp dose, were reported post-dose 1 and were considered related to study vaccine by the investigator. Post any Ad26.COV2.S administration, all fevers were reported to have started on either Day 1 (day of vaccination) or Day 2 and all resolved within a maximum of 3 days.

Unsolicited Adverse Events

The most frequently reported unsolicited AE (at least 10% in any active vaccine group) was headache during the post-dose 1 period. Post any Ad26.COV2.S dose, no unsolicited AEs of at least Grade 3 and considered related to vaccination were reported.

Other Safety Observations

The most frequent vital signs abnormalities were hypertension (systolic), increased respiratory rate, and bradycardia. A majority of reported abnormalities were Grade 1 or 2 severity. Vital sign abnormalities of Grade 3 were not considered to be AEs by the investigator, except for 2 participants who each experienced Grade 3 hypertension AE after Ad26.COV2.S vaccination (2-dose regimen [56 days] group): 1 post-dose 1 (5×10^{10} vp dose) and the other post-dose 2 (1.25×10^{10} vp dose). Both cases were considered unrelated to the study vaccine by the investigator.

Adolescents

Deaths, Serious Adverse Events, Adverse Events of Special Interest, and Adverse Events Leading to Vaccine Discontinuation

There were no SAEs or AEs with fatal outcome reported in the adolescent participants.

Two adolescent participants in the active vaccine group and none in the placebo group experienced COVID-19 related AEs.

Reactogenicity in 33 adolescents aged 16 to 17 years, vaccinated with the 2.5×10^{10} vp dose or placebo (ratio 10:1) was proportionately higher than in adults vaccinated with the 5×10^{10} vp dose.

Solicited Adverse Events

Solicited Local Adverse Events

Solicited local AEs (vaccination site pain) of Grade 3 severity were reported by 3 (10.0%) participants in the active vaccine group.

Solicited Systemic Adverse Events

Solicited systemic events were reported in 28 (93.3%) adolescent participants in the active vaccine group, the most frequently reported of which was headache (in 25 [83.3%] participants). Solicited systemic AEs of Grade 3 considered related to vaccination were recorded for 7 (23.3%) participants in the active vaccine group. Four of these 7 participants experienced more than 1 Grade 3 solicited systemic AE. This suggests relatively high reactogenicity in this age group when compared to the adult participants enroled in this trial.

Unsolicited Adverse Events

Unsolicited AEs were reported in 12/30 (40.0%) adolescent participants in the active vaccine group and 2/3 (66.7%) in the placebo group. The majority of unsolicited AEs in adolescents were Grade 1 or 2 severity. One (3.3%) adolescent participant in the active vaccine group experienced an unsolicited AE of Grade 3 or higher that was considered related to vaccination (chills).

Other Safety Observations

The most frequent vital sign abnormalities in adolescent participants were increased respiratory rate and increased pulse rate. All reported abnormalities were Grade 1 or 2 severity, except for 1 participant in the active vaccine group who had a Grade 3 increased respiratory rate (post-dose 1 follow-up) which was not considered as AE by the investigator.

There were no cases of Grade 3 pyrexia reported in adolescent participants.

Immunogenicity Summary

The immunogenicity analyses performed in adult participants in this trial showed that a single-dose of Ad26.COV2.S at 5×10^{10} vp induces humoral responses that are durable up to at least 6 months post-dose 1 (last timepoint analysed prior to a subsequent injection). The vast majority of participants had detectable antibody titers, although a trend for a decline in antibody levels was observed in ≥65-year-old participants. In each of the 2 adult age groups, a dose-response was observed. A second dose of vaccine, irrespective of dose level, induced a boost in humoral responses in adult participants. An interval of 84-days between 2 doses seemed to elicit higher neutralising and binding antibody responses post-dose 2 compared to a 56-day interval post-dose 2 in both age groups. More durable antibody responses were observed with an interval of 84-days versus 56-days. Antigen dose presentation intended to mimic SARS-CoV-2 exposure rapidly increased humoral responses by 7 and 28-days after antigen presentation (1.25×10^{10} vp Ad26.COV2.S) in all vaccine groups. However, a larger fold increase in antibody levels was observed in single dose vaccine groups compared to 2-dose vaccine groups. Six months post-antigen presentation (Day 393), all vaccine groups had similar levels of antibodies, except for the 1.25×10^{10}, 1.25×10^{10} vp (56-day) group, which tended to have lower levels.

In adolescents (16 to 17 years of age), Ad26.COV2.S administered at 2.5×10^{10} vp elicited similar peak and durable humoral responses to those observed in healthy adults 18 to 25 years of age who received Ad26.COV2.S at the 5×10^{10} vp dose level.

Conclusion

Overall, results from the safety and reactogenicity analyses showed that all evaluated doses and regimens of Ad26.COV2.S had an acceptable safety and reactogenicity profile with no significant safety issues identified in adult participants in this trial. For both the 56-day and 84-day vaccination intervals, reactogenicity post-dose 2 was generally similar to post-dose 1 with no increase observed. In addition, reactogenicity post-antigen presentation was generally similar with no increase observed compared to post-dose 1. In general, lower reactogenicity was observed for the older adults compared to the younger adults.

Based on the limited data available, the safety and reactogenicity profile of Ad26.COV2.S administered at the 2.5×10^{10} vp dose level in adolescents aged 16 to 17 years is acceptable.

Overall, the data showed that Ad26.COV2.S as a single-dose elicits humoral responses, with durable antibody responses up to at least 6 months. A rapid increase in antibody levels was observed within 7-days after administration of Ad26.COV2.S at the antigen presentation dose level of 1.25×10^{10} vp used to mimic SARS-CoV-2 exposure. This rapid increase indicates that immune memory may be established by a single-dose of Ad26.COV2.S and that such an anamnestic response may also occur in Ad26.COV2.S recipients upon SARS-CoV-2 exposure.

7.2. Ongoing Clinical Trials

An "ongoing clinical trial" is defined as a trial in which the first informed consent form has been signed, whether a hold is in place or analysis is complete, but for which a final CSR is not available at the data lock point (DLP) for this PBRER, regardless of whether the last participant last visit has occurred.

During the PBRER reporting period, 10 company-sponsored interventional clinical trials of Ad26.COV2.S (VAC31518COV1001, VAC31518COV1002, VAC31518COV1003, VAC31518COV2004, VAC31518COV2008, VAC31518COV3001, VAC31518COV3003, VAC31518COV3005, VAC31518COV3006, and VAC31518COV3009) were ongoing. A brief summary and safety findings of all ongoing clinical trials are presented below.

Trial VAC31518COV1001

This is a Phase 1/2a, randomised, double-blind, placebo-controlled, first-in-human, multicentre trial in healthy adults aged ≥18 to ≤55 years and aged ≥65 years in good health with or without stable underlying conditions to evaluate the safety, reactogenicity, and immunogenicity of Ad26.COV2.S at 2-dose levels, administered IM as a single-dose or 2-dose schedule, with a single booster vaccination administered in 1 cohort.

No significant safety findings were identified from this trial during the reporting period.

Trial VAC31518COV1002

This is a Phase 1, randomised, double-blind, placebo-controlled trial in healthy adults aged ≥20 to ≤55 years and ≥65 years in good health with or without stable underlying conditions in Japan to evaluate the safety, reactogenicity, and immunogenicity of Ad26.COV2.S at 2-dose levels, administered IM as 2-dose schedule.

No significant safety findings were identified from this trial during the reporting period.

Trial VAC31518COV1003

This is a Phase 1, randomised, observer-blind, parallel-group trial to compare the safety, reactogenicity, and immunogenicity of Ad26.COV2.S at a single-dose of 5×10^{10} vp in 2 different volumes in healthy adults aged ≥18 to ≤65 years.

No significant safety findings were identified from this trial during the reporting period.

Trial VAC31518COV2004

This is a Phase 2, open-label, multicentre trial to evaluate the safety, reactogenicity, immunogenicity, and pregnancy outcomes of Ad26.COV2.S in healthy pregnant (Second and/or Third trimester of pregnancy) participants aged ≥18 to ≤45 years.

No significant safety findings were identified from this trial during the reporting period.

Trial VAC31518COV2008

This is a Phase 2, randomised, double-blind, parallel, multicentre trial to evaluate the immunogenicity, reactogenicity, and safety of Ad26.COV2.S administered as a 1-dose booster vaccination regimen (5×10^{10} vp, 2.5×10^{10} vp or 1×10^{10} vp) in adults ≥18 years of age, who have previously received primary vaccination in Trial VAC31518COV3001 (Cohort 1 - homologous booster) or who previously received primary vaccination with the Pfizer BNT162b2 vaccine (Cohort 2 - heterologous booster).

No significant safety findings were identified from this trial during the reporting period.

Trial VAC31518COV3001

This is a Phase 3, randomised, double-blind, placebo-controlled, multicentre, pivotal efficacy, and safety trial in adults ≥18 to <60 years of age and ≥60 years of age. The efficacy, safety, and immunogenicity of Ad26.COV2.S will be evaluated in participants living in, or going to, locations with high risk for acquisition of SARS-CoV-2 infection after administration of study vaccine. All participants who initially received placebo in the double-blind phase have been offered to receive a single-dose of Ad26.COV2.S vaccine. Additionally, the open-label phase of the trial is extended to include an open-label booster vaccination with a single-dose of Ad26.COV2.S at the Year 1/Booster Visit.

No significant safety findings were identified from this trial during the reporting period.

Trial VAC31518COV3003

This is a Phase 3, randomised, double-blind trial to evaluate 6 dose levels of Ad26.COV2.S administered as a 2-dose schedule in healthy adults aged 18 to 55 years, inclusive. This trial consists of 2 parts: main trial and sub-trial. In the main trial, the safety, reactogenicity, and immunogenicity of 1 dose (dose 1 of the 2-dose regimen) and 2 doses of Ad26.COV2.S will be evaluated. In the sub-trial, additional adult participants aged 18 to 55 years will be enroled (into study groups 1, 3, 5, and 6) to further characterise the innate, pro-inflammatory, and other relevant (eg, pro-thrombotic) responses to Ad26.COV2.S to better understand a possible risk to thrombosis with TTS events.

No significant safety findings were identified from this trial during the reporting period.

Trial VAC31518COV3005

This is a Phase 3, randomised, double-blind, parallel, multicentre trial in healthy (including stable comorbidities) participants to evaluate safety, reactogenicity, and immunogenicity of Ad26.COV2.S co-administered with a seasonal quadrivalent (standard dose or high-dose) influenza vaccine. A Standard dose influenza vaccine administered to all participants with 18 years and above and high-dose influenza vaccine administered in participants with only 65 years and above compared to administration of each vaccine separately to explore whether Ad26.COV2.S and the influenza vaccines can be administered concomitantly.

No significant safety findings were identified from this trial during the reporting period.

Trial VAC31518COV3006

This is a Phase 2, randomised, observer-blind, pivotal, adaptive trial to evaluate the safety, reactogenicity, and immunogenicity of different dose levels of Ad26.COV2.S administered as a 1- or 2-dose regimen (56-day interval) in healthy adolescents aged 12 to 17 years inclusive.

No significant safety findings were identified from this trial during the reporting period.

Trial VAC31518COV3009

This is a Phase 3, randomised, double-blind, placebo-controlled, multicentre, pivotal efficacy and safety trial in adults ≥18 years of age. The efficacy, safety, and immunogenicity of Ad26.COV2.S is being evaluated in participants living in, or going to, locations with high risk for acquisition of SARS-CoV-2 infection after administration of 2 doses of study vaccine. Additionally, participants from the placebo arm enroled during the double-blind phase have been offered to receive a single-dose of Ad26.COV2.S (open-label vaccination), unless they met certain vaccination discontinuation rules during the double-blind phase of the trial. At present time, the open-label phase of the trial is extended to include an open-label booster vaccination with a single-dose of Ad26.COV2.S to all participants that have received only single-dose of Ad26COV2.S in the trial.

No significant safety findings were identified from this trial during the reporting period.

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.

7.3. Long-term Follow-up

No long-term follow-up information became available for Ad26.COV2.S during the reporting period.

7.4. Other Therapeutic Use of Medicinal Product

During the reporting period, no pre-approval patient access programmes/registries supported by the Company are ongoing or completed for Ad26.COV2.S.

7.5. New Safety Data Related to Fixed Combination Therapies

This section is not applicable as there are no marketed combination therapies with Ad26.COV2.S.

8. FINDINGS FROM NON-INTERVENTIONAL STUDIES

Based on review of the data from noninterventional study for Ad26.COV2.S during the reporting period, no new information with potential impact to the benefit-risk assessment has been identified (see Appendix 4.2).

Real World Evidence Summary for Ad26.COV2.S

The Company-sponsored (VAC31518COV4002 and VAC31518COV3021), collaborative, and publicly available real-world evidence (RWE) studies reporting on the vaccine effectiveness of Ad26.COV2.S are described below:

Study VAC31518COV4002

Interim results (up to 183 days after vaccination; median follow-up of 129 days) are available from Study VAC31518COV4002, which is an observational longitudinal post-authorisation study to assess the effectiveness of a single-dose of Ad26.COV2.S (5×10^{10} vp) in clinical practice, with onset 14 days after vaccination, in adults ≥18 years of age in the US.

The vaccine efficacy (VE) results in Janssen's large, longitudinal US cohort study demonstrated effective and stable VE for the single-dose Ad26.COV2.S, vaccine based on month-on-month analysis and Kaplan-Meier plots through the end of August 2021. There have been several other RWE studies that have been recently published by researchers, that evaluate the VE of single-dose Ad26.COV2.S vaccine. The RWE findings support and extend the conclusions of the pivotal efficacy trial. The protection against COVID-19 varies between different variants of concern. Single-dose Ad26.COV2.S VE against infection were reported to be lower during Omicron-emerging and Omicron-predominated periods. Fully vaccinated individuals who received a Ad26.COV2.S booster vaccine showed an increase in VE during the Omicron periods as reported in RWE studies. From the available literatures, it is confirmed that the benefit of a homologous or heterologous Ad26.COV2.S booster dose in protecting against COVID-19 related infections, hospitalisations, and deaths, during the Omicron period. Several factors should be considered that may influence measures of VE and limit direct study comparisons between these studies, including different study designs and outcome definitions and systematic differences in study populations such as underlying comorbidities and other risk factors, as well as demographics including socioeconomic factors. Additionally, methodological considerations such as appropriate matching of comparator cohorts, time since vaccination, follow-up times, and several other bias considerations make it difficult to directly compare point estimates for VE across studies. Despite these limitations, results from several of these real world studies are consistent

with the vaccine effectiveness seen with the single dose Ad26.COV2.S vaccine in Study VAC31518COV4002 and the booster dose Ad26.COV2.S vaccine in Study VAC31518COV3021 (refer to Section 9.1, Other Clinical Trials, for further details of Study VAC31518COV3021) (see Appendix 9.7, Supporting Data: Real World Data Analytics).

9. INFORMATION FROM OTHER CLINICAL TRIALS AND SOURCES

9.1. Other Clinical Trials

During the PBRER reporting period, 8 interventional clinical studies were ongoing: 1 interventional clinical study (COV-BOOST [VAC31518COV2009]) sponsored by the University Hospital Southampton NHS Foundation Trust, 1 interventional clinical study (VAC31518COV2012) sponsored by the Vaccine Trial Centre (Hospital for Tropical Diseases, Mahidol University, Thailand), 1 interventional clinical study (VAC31518COV2016 [AUR1-8-341]) sponsored by The Aurum Institute NPC, 2 interventional clinical studies (VAC31518COV3012 [Sisonke {Together}] and VAC31518COV3021 [Sisonke Boost Open-Label Study {SISONKE2}]) sponsored by SAMRC, 1 interventional clinical study (VAC31518COV3018) sponsored by the Mayo Clinic, 1 interventional clinical study (VAC31518COV4012) sponsored by the National and Kapodistrian University of Athens, University Research Institute of Maternal and Child Health & Precision Medicine and 1 interventional clinical study (DMID 21-0012) sponsored by NIH were ongoing for Ad26.COV2.S. Of these 8 studies, 3 (VAC31518COV2016, VAC31518COV3018, and VAC31518COV4012) were initiated during the reporting period. The summary and safety findings from these studies are presented below.

Study COV-BOOST (VAC31518COV2009)

This is a Phase 2, randomised, multicentre study conducting in the United Kingdom (UK) to determine reactogenicity and immunogenicity of booster vaccination against ancestral and novel variants of SARS-CoV-2. The study will initially consist of several cohorts enroled in 2 or 3 stages.

At the time of DLP of this PBRER, 2,878 participants were enroled, of which 206 received Ad26.COV2.S.

During the reporting period, no relevant safety information related to Ad26.COV2.S from this clinical study became available.

Study VAC31518COV2012

This is Phase 1/2, prospective, multicentre, observer-blind adaptive study to assess the safety, reactogenicity, and immunogenicity of a booster dose of Ad26.COV2.S in adults ≥18 years of age in Study Part A and Part B. A total of 478 participants were recruited. Enrolment of groups are open-label allocation and assessor-masked.

At the time of DLP of this PBRER, 478 participants received Ad26.COV2.S in this study.

During the reporting period, no new relevant safety findings related to Ad26.COV2.S from this clinical study became available.

Study VAC31518COV2016 (AUR1-8-341)

This is a Phase 2a, randomised, observer-blind, multicentre trial of the safety and immunogenicity of COVID-19 vaccine strategies in human immunodeficiency virus (HIV)-infected and HIV-uninfected adults. A total of 750 evaluable HIV-infected (660) and HIV-uninfected (90) adult participants meeting all entry criteria (all inclusion and no exclusion criteria) will be enroled in 3 treatment strategies in 3 participant groups dependent on prior vaccination with a single-dose of Janssen (Group 1), 2 doses of Pfizer (Group 2), or no prior COVID-19 vaccination with evidence of prior SARS-CoV-2 infection (Group 3).

At the time of DLP of this PBRER, 27 participants received Ad26.COV2.S in this study.

During the reporting period, no new relevant safety findings related to Ad26.COV2.S from this clinical study became available.

Study VAC31518COV3012 (Sisonke [Together])

This is a Phase 3b, open-label, single-arm, multicentre, implementation study to monitor the effectiveness of the single-dose of Ad26.COV2.S among healthcare workers (HCWs) at least 18 years of age as compared with the general unvaccinated population in South Africa. All HCWs who register on the National Vaccination Registry were eligible for enrolment.

At the time of DLP of this PBRER, 499,887 participants received Ad26.COV2.S in this study.

During the reporting period, no new relevant safety findings related to Ad26.COV2.S from this clinical study became available.

Study VAC31518COV3018

This is a Phase 3, prospective, open-label clinical trial with 1 randomised arm to evaluate the response of a heterologous additional dose with the Janssen Ad26.CoV2.S vaccine to provide vaccine induced immunity for immunocompromised kidney transplant patients after receiving 2 or more doses of the Pfizer or Moderna COVID-19 vaccine.

At the time of DLP of this PBRER, 26 participants received Ad26.COV2.S in this study.

During the reporting period, no new relevant safety findings related to Ad26.COV2.S from this clinical study became available.

Study VAC31518COV3021 (Sisonke Boost Open-label Study [SISONKE2])

This is a Phase 3b, open-label, single-arm, multicentre, implementation study in Sisonke participants in South Africa at least 18 years of age. This study will be conducted by Sisonke (VAC31518COV3012) sites in collaboration (where appropriate) with routine

National Department of Health vaccination centres in South Africa. All Sisonke participants registered on the National Vaccination Registry were eligible for enrolment, if eligibility is met.

At the time of DLP of this PBRER, 250,878 participants received Ad26.COV2.S in this study.

During the reporting period, no new relevant safety findings related to Ad26.COV2.S from this clinical study became available.

In addition, this study evaluated early VE against hospital admissions of a homologous Ad26.COV2.S boost 4 to 6 months after primary vaccination during the Omicron wave (15 November 2021 to 14 January 2022) in HCWs in South Africa (Gray 2022).VE (95% CI) against COVID-19 hospital admission was 55% (22% to74%) when evaluated 0 to 13 days after the booster and increased to 74% (57% to 84%) when evaluated 14 to 27 days and 72% (59% to 81%) 1 to 2 months after the booster. These results provide the first evidence of effectiveness against COVID-19 hospital admissions of a homologous Ad26.COV2.S booster given 4 to 6 months after single dose primary vaccination during a period of Omicron variant circulation (refer to Section 8, Findings from Non-interventional Studies for more information about booster vaccine effectiveness from this study).

Study VAC31518COV4012

This a study in individuals >18 years of age to investigate the association of total antibodies, neutralising antibodies, and T-cell responses against SARS-CoV-2 spike protein with epidemiological and clinical parameters in a cohort of vaccinees after initial immunisation with the Ad26.COV2.S vaccine and boosting with either Ad26.COV2.S vaccine or messenger Ribonucleic Acid (mRNA) vaccines. In addition, to investigate the initial antibody response 1 month after immunisation and then to follow the antibody kinetics during a 1-year period and the T-cell responses with sequencing to the T-cell repertoire after initial immunisation with Ad26.COV2.S vaccine and boosting with either Ad26.COV2.S vaccine or mRNA vaccines.

At the time of DLP of this PBRER, 270 participants received Ad26.COV2.S in this study.

During the reporting period, no new relevant safety findings related to Ad26.COV2.S from this clinical study became available.

Study DMID 21-0012

This is a Phase 1/2, open-label study in individuals, 18 years of age and older, who are in good health, have no known history of COVID-19 or SARS-CoV-2 infection, and meet all other eligibility criteria. 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 manufactured by ModernaTX, Inc.; BNT162b2 manufactured by Pfizer/BioNTech; or Ad26.COV2.S manufactured by Janssen Pharmaceuticals/Johnson & Johnson).

At the time of DLP of this PBRER, 150 participants 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.

Overall, no significant safety findings from other clinical trials/studies were identified during the reporting period that had an impact on the benefit-risk balance of Ad26.COV2.S.

9.2. Medication Errors

Introduction

Cases of medication errors or potential medication errors are reviewed in all COVID-19 vaccine PBRERs. Medication error is synonymous with vaccination error.

Methods

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).[15]

Results/Discussion

Primary Dose

During the reporting period of 25 February 2022 to 24 August 2022, 172 (146 medically confirmed and 26 medically unconfirmed) initial, primary dose cases reporting medication errors were identified. Of these 172 cases, 9 were serious and 163 were nonserious and reported a total of 294 events (4 serious; 290 nonserious) of medication errors.

Of these 172 initial, primary dose cases reported during the reporting period of 25 February 2022 to 24 August 2022, 1 was reported from a Janssen Sponsored Clinical Study and 171 were from post-marketing sources (including spontaneous and solicited cases). No cases were retrieved from Janssen Supported Clinical Studies.

Cumulatively, 2,489 (1,774 medically confirmed and 715 medically unconfirmed) primary dose cases reporting medication errors were identified. Of these cases, 174 cases were serious and 2,315 were nonserious and reported a total of 3,241 events (46 serious; 3,195 nonserious) of medication errors.

[15] Of note, the use of the SMQ Medication errors (broad) includes PTs, such as Product use in unapproved indication and Product administered to patient of inappropriate age, that could be used to describe off label use. However, these terms could also involve accidental use and are, therefore, included for completeness. It should be noted that the PT Off label use is not included in the SMQ Medication errors (broad) and since off label use may be considered as intentional, these cases will not be analysed in this section; however, for transparency reasons the cases containing this term are included in this section.

Of the 2,489 cumulative primary dose cases received, 7 were reported from Janssen Sponsored Clinical Studies, 24 from Janssen Supported Clinical Studies, and 2,458 from post-marketing sources (including spontaneous and solicited cases).

Booster Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 339 (82 medically confirmed and 257 medically unconfirmed) initial cases reported as booster were identified. There were 45 serious and 294 nonserious cases and reported a total of 348 events (10 serious; 338 nonserious) of medication errors. Of these cases, 187 were heterologous and 152 were homologous.

Of these 339 initial cases reported as booster during the interval, 2 were reported from Janssen Sponsored Clinical Studies and 337 from post-marketing sources (including spontaneous and solicited). No cases were retrieved from Janssen Supported Clinical Studies.

Cumulatively, 1,071 (279 medically confirmed and 792 medically unconfirmed) cases reported as booster were identified. Of these cases, 83 cases were serious and 988 were nonserious and reported a total of 1,112 events (17 serious; 1,095 nonserious) of medication errors. Of these cases, 688 were homologous and 383 were heterologous.

Of the 1,071 cumulative cases reported as booster, 2 were reported from Janssen Sponsored Clinical Studies and 1,069 from post-marketing sources (including spontaneous and solicited cases). No cases were retrieved from Janssen Supported Clinical Studies.

A cumulative booster dose Council for International Organisation of Medical Sciences (CIOMS) II Line Listing (LL) is presented in Appendix 6.1.

Clinical Trial Cases

Primary Dose

Janssen Sponsored Clinical Studies

During the reporting period of 25 February 2022 to 24 August 2022, 1 initial, primary dose case reporting medication error was retrieved from a Janssen Sponsored Clinical Study. This case was from Study VAC31518COV3009 and concerned a 40-year-old female from [redacted] who experienced a serious event of overdose not related to Ad26.COV2.S (polypharma overdose on different unspecified tablets). The outcome for the event was reported as resolved.

Janssen Supported Clinical Studies

There were no initial primary dose cases retrieved from the search of the Company global safety database during the reporting period of 25 February 2022 to 24 August 2022.

Booster Dose

Janssen Sponsored Clinical Studies

During the interval reporting period of 25 February 2022 to 24 August 2022, 2 initial cases reported as booster were retrieved from Janssen Sponsored Clinical Studies. Both cases were from Study VAC31518COV3001. The reported medication errors included drug delivery system malfunction and overdose (n=1 each), which did not refer to Ad26.COV2.S, but to insulin pump malfunction and to an unspecified drug overdose, which was treated with activated charcoal and naloxone.

Janssen Supported Clinical Studies

There were no initial cases reported as booster which were retrieved from the search of the Company global safety database during the interval reporting period of 25 February 2022 to 24 August 2022.

Post-marketing Sources (Including Spontaneous and Solicited Cases)

Primary Dose

During the reporting period of 25 February 2022 to 24 August 2022, 171 (145 medically confirmed and 26 medically unconfirmed) post-marketing sources (including spontaneous and solicited), initial, primary dose cases reporting medication errors were retrieved. Of these 171 cases, 12 concerned paediatric patients and are discussed in subsection 9.2.1, Paediatric Cases below. The remaining 159 post-marketing, primary dose cases reported 278 events (2 serious; 276 nonserious) of medication errors.

Cumulatively, 2,458 (1,743 medically confirmed and 715 medically unconfirmed) post-marketing, primary dose cases reporting medication errors were identified. Of these 2,458 cases, 371 concerned paediatric patients and are discussed in subsection 9.2.1, Paediatric Cases below. The remaining 2,087 post-marketing, primary dose cases reported a total of 2,810 events (32 serious; 2,778 nonserious) of medication error.

An overview of these cases is presented in Table 11 below.

Table 11: Characteristics of Post-marketing, Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Medication Errors

Case Characteristics		Number of Cases Received During the Reporting Period=159	Number of Cases Received Cumulatively=2,087
Sex	Male	56	697
	Female	51	672
	NR	52	718
Age (Years)[a]	18 to 35	32	314
Minimum: 18	36 to 50	33	297
	51 to 64	31	345

Table 11: Characteristics of Post-marketing, Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Medication Errors

Case Characteristics		Number of Cases Received During the Reporting Period=159	Number of Cases Received Cumulatively=2,087
Maximum: 83	≥65	9	183
Mean: 44.3	Adult	0	40
Median: 44	Elderly	2	7
	NR	52	901
Sources	Spontaneous	157	2,076
	Clinical study (noninterventional; solicited)	2	10
	Clinical Study (noninterventional; unsolicited)	0	1
Country/Territory[b]	United States	148	1,794
	Germany	2	39
	Poland	2	20
	Brazil	1	17
	Canada	1	8
	France	1	72
	Netherlands	1	10
	Philippines	1	2
	Switzerland	1	2
	United Kingdom	1	2
Event Characteristics		**Number of Events=278**	**Number of Events=2,810**
Seriousness (Event Level)[c]	Nonserious	276	2,778
	Serious	2	32
Outcome (Event Level)[c]	Resolved	3	48
	Not resolved	1	34
	Resolved with sequelae	1	1
	Resolving	1	5
	Fatal	0	1
	NR	272	2,721

Key: NR=Not Reported

a: The calculation was based on the current reporting period (25 February 2022 to 24 August 2022). Age group was presented for cases where age was not reported.

b: Countries/Territories were presented in decreasing order for the current reporting period (25 February 2022 to 24 August 2022).

c: Seriousness and outcome have been presented for the events of interest. A single case may report more than 1 event of interest.

Of these 159 post-marketing, initial, primary dose cases received during the reporting period, the most frequently (n≥50) reported country/territory of origin was the US (n=148). These cases concerned 56 males, 51 females, and 52 did not report sex. The age range was from 18 to 83 years.

The frequency distribution of the MedDRA PTs of interest reported in post-marketing, primary dose cases (n=159) is presented in Table 12 below. A single case may contain more than 1 event

of interest (EOI). The majority of the cases included the PT of Expired product administered, Poor quality product administered, and/or Product storage error, and reflected that either the vaccine was administered beyond the expiration date, or after incorrect storage (temperature excursion or vaccine being drawn from a punctured vial kept beyond the recommended storage time).

Table 12: Frequency of MedDRA PTs of Interest in Post-marketing, Primary Dose Cases Reporting Medication Errors With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Poor quality product administered	0	119	0	696
Product storage error	0	119	2	582
Inappropriate schedule of product administration	0	13	1	94
Expired product administered	0	10	4	513
Product administered at inappropriate site	1	1	2	16
Product administered to patient of inappropriate age	0	2	0	11
Underdose	0	2	1	105
Wrong technique in product usage process	0	2	0	29

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: The MedDRA PTs of interest with a frequency ≥2 have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event of interest.

Of the 159 post-marketing initial, primary dose cases retrieved during the reporting period, 12% (19/159) of cases reported the PT of Off label use.

The majority (86.2%; 137/159) of post-marketing initial, primary dose cases involved medication errors without any additional AEs reported (classified as error without harm); whereas 13.8% (22/159) of cases reported medication errors with harm. These 22 cases reported 85 additional AEs (34 serious; 51 nonserious). The most frequently reported events of medication errors in these cases (n≥2) were inappropriate schedule of product administration (n=10), and product administered at inappropriate site, product administered to patient of inappropriate age, and wrong technique in product usage process (n=2 each).

The frequency distribution of additional AEs (n≥2) reported in 22 post-marketing, primary dose cases reporting medication errors with harm with the use of Ad26.COV2.S is presented in Table 13 below. Most of the AEs were nonserious and presented local and systemic reactogenicity to Ad26.COV2.S.

Table 13: Frequency Distribution of Additional AEs in Post-marketing, Primary Dose Cases Involving Use of Ad26.COV2.S and Reporting Medication Errors With Harm

Additional AEs	Number of Events Received During the Reporting Period[a,b]		Number of Events Received Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Fatigue	1	3	10	80
Chills	1	2	4	65
COVID-19	0	3	5	10
Headache	0	3	11	99
Limb discomfort	1	2	2	8
Pain in extremity	1	2	8	73
Arthralgia	1	1	4	30
Condition aggravated	1	1	2	2
Dizziness	1	1	6	29
Hyperhidrosis	1	1	5	15
Myalgia	0	2	4	36
Nausea	1	1	4	41
Pyrexia	0	2	7	88

Key: AE=Adverse Event; COVID-19=Coronavirus Disease-2019

a: A single case may report more than 1 additional AE. Additional AEs with frequency ≥2 have been presented.

b: Additional AEs were sorted by descending frequency for the reporting period (25 February 2022 to 24 August 2022).

Fatal Post-marketing Primary Dose Cases

There were no fatal post-marketing primary dose cases retrieved from the search of the Company global safety database during the interval reporting period of 25 February 2022 to 24 August 2022.

Booster Dose

During the reporting period of 25 February 2022 to 24 August 2022, 337 (80 medically confirmed and 257 medically unconfirmed) post-marketing sources (including spontaneous and solicited), initial cases reported as booster were retrieved. Of these 337 cases, 5 concerned paediatric patients which are discussed in subsection 9.2.1, Paediatric Cases below. The remaining 332 post-marketing booster dose cases reported 340 events (8 serious; 332 nonserious) of medication errors.

Cumulatively, 1,069 (277 medically confirmed and 792 medically unconfirmed) post-marketing, cases reported as booster were identified. Of these 1,069 cases, 7 concerned paediatric patients and are discussed in subsection 9.2.1, Paediatric Cases below. The remaining 1,062 post-marketing booster dose cases reported a total of 1,100 events (15 serious; 1,085 nonserious) of medication errors.

An overview of these cases is presented in Table 14 below.

Table 14: Characteristics of Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Medication Errors

Case Characteristics		Number of Cases Received During the Interval Reporting Period=332	Number of Cases Received Cumulatively=1,062
Sex	Female	202	521
	Male	121	497
	NR	9	44
Age (Years)[a]	18 to 35	56	214
Minimum: 18	36 to 50	73	264
Maximum: 91	51 to 64	61	181
Mean: 49.4	≥65	53	151
Median: 48	Adult	3	8
	Elderly	2	3
	NR	84	241
Country/Territory[b]	Brazil	237	421
	United States	33	454
	Canada	18	37
	South Africa	12	21
	Colombia	9	21
	Germany	7	24
	Korea, Republic of	5	23
	Iceland	4	4
Sources	Spontaneous	289	741
	Clinical study (noninterventional; solicited)	35	312
	Clinical study (noninterventional; unsolicited)	8	9
Classification	Heterologous	185	381
	Homologous	147	681
Event Characteristics		**Number of Events=340**	**Number of Events=1,100**
Seriousness (Event Level)[c]	Nonserious	332	1,085
	Serious	8	15
Outcome (Event Level)[c]	Fatal	2	3
	Not resolved	1	5
	Resolved	1	6
	NR	336	1,086

Key: NR=Not Reported

a: The calculation was based on the current reporting period (25 February 2022 to 24 August 2022). Age group was presented for cases where age was not reported.

b: Countries/Territories with frequency ≥4 have been presented in decreasing order for the current reporting period (25 February 2022 to 24 August 2022).

c: Seriousness and outcome have been presented for the events of interest. A single case may report more than 1 event of interest.

Of these 332 post-marketing initial cases reported as booster received during the reporting period, the most frequently reported countries/territories of origin (≥30) were Brazil (n=237), followed by

the US (n=33). These cases concerned 202 females, 121 males, and 9 did not report sex. The age range was from 18 to 91 years.

The frequency distribution of the MedDRA PTs of interest reported in post-marketing cases reported as booster is presented in Table 15 below. A single case may contain more than 1 EOI.

Table 15: Frequency of MedDRA PTs of Interest in Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Medication Errors

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Inappropriate schedule of product administration	0	311	0	877
Interchange of vaccine products	6	3	12	8
Product storage error	0	5	0	13
Poor quality product administered	0	4	0	19
Underdose	1	2	1	73
Incorrect route of product administration	0	2	0	5
Wrong product administered	1	1	1	3
Wrong technique in product usage process	0	2	0	4
Extra dose administered	0	1	0	3
Product use issue	0	1	0	1

Key: MedDRA=Medical Dictionary for Regulatory Activities; n=Number; PT=Preferred Term
a: The MedDRA PTs of interest are sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event of interest.

As displayed in Table 15, the most frequently reported PT for this reporting period was Inappropriate schedule of product administration (n=311) which mainly was reported in patients who received a booster dose in the off label use setting (n=305). Most of these cases originated from Brazil (n=234), where approval of Ad26.COV2.S occurred during the reporting interval of the current PBRER (05 April 2022).

Of the 332 post-marketing sources (including spontaneous and solicited) initial cases reported as booster, the majority (84.03%; 279/332) of them contained additional AEs (classified as medication errors with harm).

The frequency distribution of additional AEs (n≥10) reported in these cases is presented in Table 16 below. The most frequently reported events were nonserious and represented local and systemic reactogenicity to Ad26.COV2.S. and adverse reactions of hypersensitivity.

Table 16: Frequency Distribution of Additional AEs in Post-marketing Cases Reported as Booster Involving Use of Ad26.COV2.S and Reporting Medication Errors With Harm

Additional AEs	Number of Events Received During the Reporting Period[a,b]		Number of Events Received Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Pyrexia	0	95	0	200
Headache	1	78	2	170
Pain	1	68	1	127
Pain in extremity	0	37	3	67
Chills	0	35	0	100
Fatigue	0	34	0	110
Malaise	1	27	2	48
Asthenia	0	26	1	41
Injection site pain	0	24	0	67
Feeling abnormal	0	22	1	35
Dizziness	0	21	0	57
Arthralgia	1	19	2	49
Vaccination site pain	0	20	0	39
Dyspnoea	0	17	2	44
Nausea	0	17	2	57
Paraesthesia	0	16	1	29
Myalgia	0	14	0	103
COVID-19	3	9	6	21
Pruritus	1	11	1	24
Tremor	0	12	0	15
Erythema	0	11	1	18
Hypersensitivity	0	11	0	16
Peripheral swelling	0	11	1	12
Application site pain	0	10	0	18
Illness	0	10	0	13
Rash	1	9	2	14
Swelling	0	10	0	12

Key: AE=Adverse Event; COVID-19=Coronavirus Disease-2019

a: A single case may report more than 1 additional AEs. Additional AEs with frequency ≥10 have been presented.

b: Additional AEs were sorted by descending frequency for the reporting period (25 February 2022 to 24 August 2022).

Fatal Post-marketing Booster Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 3 fatal cases reported as booster were retrieved, referring to a 60-year-old patient and 2 patients with unknown age. Reported causes of death were myocardial infarction (n=1), an unspecified adverse event (n=1) and thrombosis, haemorrhage and myocardial infarction (n=1), this case is also included in the analysis of cases with Coronary Artery Disease, see Section 16.3.6.1.3 All 3 cases lacked information for an adequate medical assessment, including medical history, latency, nature and/or clinical course of the reported fatal AEs.

9.2.1. Paediatric Cases

Results/Discussion

Post-marketing Sources (Including Spontaneous and Solicited Cases)

Primary Dose

During the reporting period of 25 February 2022 to 24 August 2022, 12 (9 medically confirmed and 3 medically unconfirmed) post-marketing sources (including spontaneous and solicited), initial, primary dose cases reporting medication errors in paediatric population were retrieved. These 12 post-marketing, initial, primary dose cases reported 15 events (1 serious; 14 nonserious) of medication errors.

Cumulatively, 371 (193 medically confirmed and 178 medically unconfirmed) post-marketing, primary dose cases reporting medication errors in paediatric population were identified. Of these cases, 23 cases were serious and 348 were nonserious and reported a total of 400 events (7 serious; 393 nonserious) of medication errors.

An overview of these cases is presented in Table 17 below. The majority of the cases involved adolescent patients (n=11).

Table 17: Characteristics of Post-marketing, Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Medication Errors in Paediatric Population

Case Characteristics		Number of Cases Received During the Reporting Period=12	Number of Cases Received Cumulatively=371
Sex	Male	6	186
	Female	5	132
	NR	1	53
Age (Years)[a]	≤11	0	6
Minimum: 12	12 to 17	11	346
Maximum: 17	Adolescent	0	13
Mean: 14.7	Child	1	6
Median: 16			
Sources	Spontaneous	10	367
	Clinical study (noninterventional; solicited)	2	4
Country/Territory[b]	United States	5	171
	Canada	2	3
	South Africa	2	3
	Brazil	1	1
	Greece	1	3
	Portugal	1	7

Table 17: Characteristics of Post-marketing, Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Medication Errors in Paediatric Population

Case Characteristics		Number of Cases Received During the Reporting Period=12	Number of Cases Received Cumulatively=371
Event Characteristics		**Number of Events=15**	**Number of Events=400**
Seriousness (Event Level)[c]	Nonserious	14	393
	Serious	1	7
Outcome (Event Level)[c]	Not resolved	0	1
	NR	15	399

Key: NR=Not Reported

a: The calculation was based on the current reporting period (25 February 2022 to 24 August 2022). Age group was presented for cases where age was not reported.

b: Countries/Territories were presented in decreasing order for the current reporting period (25 February 2022 to 24 August 2022).

c: Seriousness and outcome have been presented for the events of interest. A single case may report more than 1 event of interest.

Of these 12 post-marketing initial, primary dose paediatric cases, the most frequently (n≥5) reported country/territory of origin was the US (n=5). These cases concerned 6 males, 5 females, and 1 did not report sex.

The frequency distribution of the MedDRA PTs of interest reported in post-marketing, primary dose paediatric cases is presented in Table 18 below. A single case may contain more than 1 EOI. The most frequently reported medication error PT was Product administered to patient of inappropriate age. The PT of "Circumstance or information capable of leading to medication error" referred to a mistake in the patient's record, rather than a vaccination error.

Table 18: Frequency of MedDRA PTs of Interest in Post-marketing, Primary Dose Cases Reporting Medication Errors in Paediatric Population With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Product administered to patient of inappropriate age	0	11	3	341
Circumstance or information capable of leading to medication error	1	0	1	0
Incorrect dose administered	0	1	0	1
Poor quality product administered	0	1	0	4
Product use issue	0	1	0	20

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

a: The MedDRA PTs of interest are sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event of interest.

Of the 12 post-marketing initial, primary dose paediatric cases retrieved during the reporting period, the majority (83.3%; 10/12) of the cases reported the PT of Off label use.

More than half (66.7%; 8/12) of the post-marketing initial, primary dose paediatric cases involved medication errors without harm, ie, no additional AEs were reported. In the remaining 4 out of the 12 cases, 20 additional AEs (all nonserious) were reported.

The frequency distribution of additional AEs reported in post-marketing, primary dose cases reporting medication errors with harm in paediatric population with the use of Ad26.COV2.S is presented in Table 19 below. The majority of the reported events represented local or systemic reactogenicity to Ad26.COV2.S.

Table 19: Frequency Distribution of Additional AEs in Primary Dose Cases Involving Use of Ad26.COV2.S and Reporting Medication Errors in Paediatric Population

Additional AEs	Number of Events Received During the Reporting Period[a,b]		Number of Events Received Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Pyrexia	0	3	2	44
Pain	0	2	1	7
Bedridden	0	1	0	1
Chest pain	0	1	0	1
Chills	0	1	1	14
COVID-19	0	1	0	3
Erythema	0	1	0	1
Fatigue	0	1	0	12
Headache	0	1	0	40
Illness	0	1	0	2
Lymphadenitis	0	1	0	1
Malaise	0	1	1	8
Musculoskeletal disorder	0	1	0	1
Nasopharyngitis	0	1	0	1
Nausea	0	1	0	7
Pruritus	0	1	0	1
Swelling	0	1	0	2

Key: AE=Adverse Event; COVID-19=Coronavirus Disease-2019
a: A single case may report more than 1 additional AE.
b: Additional AEs were sorted by descending frequency for the reporting period (25 February 2022 to 24 August 2022).

Fatal Post-marketing Primary Dose Cases

There were no fatal post-marketing primary dose cases retrieved from the search of the Company global safety database during the interval reporting period of 25 February 2022 to 24 August 2022.

Booster Dose

During the reporting period of 5 February 2022 to 24 August 2022, 5 post-marketing sources (including spontaneous and solicited), initial cases reported as booster which reported

medication errors in paediatric population were retrieved. These 5 post-marketing, initial, booster dose cases reported 6 events (no serious; 6 nonserious) of medication errors.

Cumulatively, 7 (4 medically confirmed and 3 medically unconfirmed) post-marketing cases reported as booster which reported medication errors in paediatric population were identified. Of these cases, 1 was serious and 6 were nonserious and reported a total of 10 events (no serious; 10 nonserious) of medication errors.

An overview of these cases is presented in Table 20 below.

Table 20: Characteristics of Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Medication Errors in Paediatric Population

Case Characteristics		Number of Cases Received During the Interval Reporting Period=5	Number of Cases Received Cumulatively=7
Sex	Female	3	4
	Male	2	3
Age (Years)[a] **Minimum: 13** **Maximum: 17** **Mean: 14.8** **Median: 14**	12 to 17	5	7
Country/Territory[b]	Brazil	4	4
	Canada	1	1
Sources	Spontaneous	4	6
	Clinical study (noninterventional; solicited)	1	1
Classification	Heterologous	2	2
	Homologous	3	5
Event Characteristics		**Number of Events=6**	**Number of Events=10**
Seriousness (Event Level)[c]	Nonserious	6	10
Outcome (Event Level)[c]	NR	6	10

Key: NR=Not Reported

a: The calculation was based on the current reporting period (25 February 2022 to 24 August 2022).

b: Countries/territories were presented in decreasing order for the current reporting period (25 February 2022 to 24 August 2022).

c: Seriousness and outcome have been presented for the events of interest. A single case may report more than 1 event of interest.

Of these 5 post-marketing, initial cases reported as booster, the most frequently (n≥4) reported country/territory of origin was Brazil (n=4). These cases concerned 3 females and 2 males. The age range was from 13 to 17 years.

The frequency distribution of the MedDRA PTs of interest reported in post-marketing, initial cases reported as booster in paediatric population is presented in Table 21 below. A single case may contain more than 1 EOI.

Table 21: Frequency of MedDRA PTs of Interest in Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Medication Errors in Paediatric Population

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Product administered to patient of inappropriate age	0	5	0	7
Inappropriate schedule of product administration	0	1	0	1

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: The MedDRA PTs of interest are sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event of interest.

Of the 5 post-marketing, initial cases reported as booster in paediatric population retrieved during the reporting period, the majority (80%; 4/5) reported the PT of Off label use and the majority (80%, 4/5) of the cases reported additional AEs.

The frequency distribution of additional AEs reported in these 5 cases is presented in Table 22 below. All serious events were reported in 1 medically unconfirmed case, which concerned a 13-year-old male with underlying autism and multiple allergies, who was also on concomitant medications of risperidone and amitriptyline. The patient was administered a primary dose of tozinameran and within 2 to 6 weeks took an Ad26.COV2.S booster dose instead of tozinameran by mistake. The patient was hospitalised within 24 hours post-booster dose and was reported to have cardiac ischaemia and renal failure (medically unconfirmed). In the absence of a clear diagnosis, and the presence of confounding medications (antipsychotics, which can have similar effects), an adequate causality assessment could not be performed.

Table 22: Frequency Distribution of Additional AEs in Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Medication Errors With Harm in Paediatric Population

Additional AEs	Number of Events Received During the Reporting Period[a,b]		Number of Events Received Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Headache	0	2	0	2
Abdominal pain upper	1	0	1	0
Application site discolouration	0	1	0	1
Arrhythmia	1	0	1	0
Axillary mass	0	1	0	1
Depressed mood	0	1	0	1
Fatigue	0	1	0	1

Table 22: Frequency Distribution of Additional AEs in Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Medication Errors With Harm in Paediatric Population

Additional AEs	Number of Events Received During the Reporting Period[a,b]		Number of Events Received Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Muscle spasms	1	0	1	0
Myocardial ischaemia	1	0	1	0
Nausea	1	0	1	0
Pyrexia	1	0	1	0
Renal failure	1	0	1	0
Vomiting	1	0	1	0

Key: AE=Adverse Event; COVID-19=Coronavirus Disease-2019
a: A single case may report more than 1 Additional AEs.
b: Additional AEs of interest were sorted by descending frequency for the reporting period (25 February 2022 to 24 August 2022).

Fatal Post-marketing Booster Dose Cases

There were no fatal post-marketing cases reported as booster retrieved from the search of the Company global safety database during the interval reporting period of 25 February 2022 to 24 August 2022.

Discussion

Overall, the majority of primary dose cases with medication errors involved use of expired product or product that was stored inappropriately. Most of these cases did not report AEs. Of the booster dose cases, the majority reported the PT of Inappropriate schedule of product administration, largely in the off label use setting and hence did not represent true errors. Reported AEs in all cases with medication errors usually were nonserious and represented reactogenicity to Ad26.COV2.S, without evidence for a causal association of AEs to the reported errors. No safety concern arose from review of the paediatric initial and booster dose cases.

Conclusion

No new safety issues were identified through review of cases reporting medication errors including paediatric cases. Overall, no new patterns of cases reporting medication errors or potential medication errors were identified. The CCDS contains information for the provider on indication, proper administration, and storage of the vaccine.

10. NON-CLINICAL DATA

During the period covered by this report, no new nonclinical safety concerns were identified for Ad26.COV2.S.

11. LITERATURE

The Company periodically conducts comprehensive searches of the scientific databases MEDLINE® and Embase®, which also includes abstracts presented at scientific meetings, to identify safety and/or efficacy information that may affect or further inform the benefit-risk profile

of Ad26.COV2.S. It should be noted that the literature searches are wider than those for individual case safety reports (ICSRs) and include studies reporting safety outcomes in groups of subjects. The search also includes information relevant to other similar vaccines and vaccine components such as stabilisers, preservatives and adjuvants.

The Company focuses the evaluation of the literature references yielded from these searches on new and significant safety findings for previously known safety concerns, as well as unidentified safety and/or efficacy concerns from other safety topics. Published literature generated from MAH sponsored interventional clinical trials retrieved from these searches are not included in this section as any new, important findings are evaluated as part of the clinical trial programme and are included in Section 7, Summaries of Significant Findings From Clinical Trials During the Reporting Interval of this PBRER or have been included in Section 7 in a previous PBRER. Similarly, any literature references that meet ICSR criteria are entered into the Company global safety database and are evaluated in Sections 15 and 16.3 of the PBRER for any new or significant safety findings that may impact safety topics. Unless additional safety information (apart from ICSR) is included, these literature references are not presented in this section of the PBRER.

In addition, if the Company becomes aware of new safety/efficacy information from unpublished abstracts/manuscripts these would also be considered for evaluation and the findings will be discussed.

Selected references and Sponsor Comments are presented below.

11.1. Product-Specific Literature

Anastassopoulou C, Hatziantoniou S, Vlachopoulos C, et al. Temporal relationship of myocarditis and pericarditis following COVID-19 vaccination: A pragmatic approach. *Int. J. Cardiol.* 2022.

Background: Complications following COVID-19 vaccination, particularly with mRNA vaccines, rarely include myocarditis and pericarditis. This work principally aimed at defining a realistic temporal relationship between vaccination and myocarditis/pericarditis development.

Method: All relevant cases reported from week 52/2020 through week 41/2021 in the VAERS database were retrieved and analysed for licensed vaccines. These included BNT162b2, mRNA-1273, and AD26.COV2.S. Incidence rates were calculated using the corresponding administered vaccine doses as denominators. Additionally, analysed parameters included demographics, dose series, hospitalisation length, and outcome.

Results: Overall, 2,016 myocarditis and 1,380 pericarditis cases, ($4.96/10^6$ and $3.40/10^6$ administered vaccine doses, respectively), were recorded. Most myocarditis cases occurred following BNT162b2 ($5.60/10^6$ doses) in males <30 years. Pericarditis affected predominantly males <40, both sexes >40 years, and was most common post AD26.COV2.S ($4.78/10^6$ doses). Hospitalisation was required for 40.3% and 27.2% of myocarditis and pericarditis cases, respectively. A bimodal pattern was found for both myocarditis and pericarditis, with 2 peaks that coincided temporally, but were reversed in intensity. The first peak was recorded 1 to 3 days post-vaccination and was more pronounced in myocarditis, while the second was recorded 15 to 30 days post-vaccination and was more intense in pericarditis.

Conclusion: Myocarditis/pericarditis after COVID-19 vaccination is rare and depicts a bimodal pattern.

MAH Comments: As summarised by the authors, "*Most myocarditis cases occurred following BNT162b2 (5.60/10^6 doses) in males <30 years. Pericarditis affected predominantly males <40, both sexes >40 years, and was most common post AD26.COV2.S (4.78/10^6 doses).*" Myocarditis and pericarditis have been closely monitored by the Company. Based on the cumulative review of the totality of the Ad26.COV2 data, the Company considered that the available data was insufficient to establish a causal association between Ad26.COV2.S and myocarditis/pericarditis. The Company will continue to closely monitor cardiac inflammatory disorders as an AESI. No new safety signal was identified.

Frontera JA, Tamborska AA, Doheim MF, et al. Neurological Events Reported after COVID-19 Vaccines: An Analysis of VAERS. *Ann. Neurol.* 2022.

Objective: To identify the rates of neurological events following administration of mRNA (Pfizer, Moderna) or adenovirus vector (Janssen) vaccines in the US.

Methods: We utilised publicly available data from the US VAERS collected between 01 January 2021 to 01 June 2021. All free text symptoms that were reported within 42 days of vaccine administration were manually reviewed and grouped into 36 individual neurological diagnostic categories. Post-vaccination neurological event rates were compared between vaccine types and to age-matched baseline incidence rates in the US and rates of neurological events following COVID-19.

Results: Of 306,907,697 COVID-19 vaccine doses administered during the study timeframe, 314,610 (0.1%) people reported any AE and 105,214 (0.03%) reported neurological AEs in a median of 1 day (IQR0 to 3) from inoculation. GBS, and cerebral venous thrombosis (CVT) occurred in fewer than 1 per 1,000,000 doses. Significantly more neurological AEs were reported following Janssen (Ad26.COV2.S) vaccination compared to either Pfizer-BioNtech (BNT162b2) or Moderna (mRNA-1273; 0.15% versus 0.03% versus 0.03% of doses, respectively P<0.0001). The observed-to-expected (O/E) ratios for GBS, CVT, and seizure following Janssen vaccination were >=1.5-fold higher than background rates. However, the rate of neurological events after acute SARS-CoV-2 infection was up to 617-fold higher than after COVID-19 vaccination.

Conclusion: Reports of serious neurological events following COVID-19 vaccination are rare. GBS, CVT, and seizure may occur at higher than background rates following Janssen vaccination. Despite this, rates of neurological complications following acute SARS-CoV-2 infection are up to 617-fold higher than after COVID-19 vaccination.

MAH Comments: GBS, transverse myelitis, and thrombosis in combination with thrombocytopenia are known risks described in Section 4.4 (special warning and precaution) and Section 4.8 (undesirable effects) of the Summary of Product Characteristics (SmPC) for Ad26.COV2.S vaccine (Janssen COVID-19 vaccine SmPC 2021). Regarding seizures, the authors state that their findings "*are considered exploratory, however, since syncope or convulsive syncope may be confused with seizure. Without access to the source medical records, we cannot infer causality;*" Regarding the presented acute disseminated encephalomyelitis and meningoencephalitis (ADEM) data, the authors importantly point out "*the wide confidence intervals (which cross 1.0)*" No new safety information is detected at this time.

Kyungu FM, Katumba AM, Kamwira HL, et al. Acute acalculous cholecystitis following COVID-19 vaccination: a case report. *Pan Afr. Med. J.* 2022; 41:291.

Abstract: Acute acalculous cholecystitis is an acute inflammation of the gallbladder in the absence of stones, usually occurring in elderly and critically ill patients with underlying conditions. A 29-year-old man presented to the hospital complaining of abdominal pain in the right hypochondrium with

permanent fever, 3 days after Janssen COVID-19 vaccine inoculation. Abdominal ultrasound revealed a thickened gallbladder wall without evidence of gallstone consistent of an acute acalculous cholecystitis. Blood analyses revealed thrombocytopenia, eosinophilia and liver dysfunction. The Polymerase Chain Reaction (PCR) COVID-19 test was negative. As treatment, the patient benefited of pain management, antibiotic, and fluid. In the evolution, there was a regression of clinical signs with persistence of liver dysfunction. The patient was discharged 10 days after hospitalisation. The Janssen COVID-19 vaccine is likely to induce acute acalculous cholecystitis as AE following vaccination.

MAH Comment: "*Acalculous cholecystitis is an acute necroinflammatory disease of the gallbladder with a multifactorial pathogenesis. It accounts for approximately 10 percent of all cases of acute cholecystitis and is associated with high morbidity and mortality rates. [...] Pathologically in patients with acalculous cholecystitis, endothelial injury, gallbladder ischemia, and stasis, lead to concentration of bile salts, gallbladder distension, and eventually necrosis of the gallbladder tissue.*"[16] According to the published literature[17], some cases of acalculous cholecystitis have been reported after COVID-19 infection. The current case reported a "*previously healthy*" young man "*without underlying medical conditions*" who experienced the symptoms 3 days after vaccination. Although ultrasound examination revealed thickened gall bladder measuring approximately 7.7 mm without evidence of gallstones, as well as laboratory results revealed thrombocytopenia, eosinophilia, and liver dysfunction; however, an association to vaccination cannot be ascertained in this case. It was missing some data on full work-up for infections and differential diagnosis. No new safety signal is identified at this time.

Lareb.nl. Decreased milk supply during breastfeeding after COVID-19 vaccination. 2022.

No abstract available.

MAH Comment: "*In 2021, Lareb received nearly 200 reports from women who had noticed [temporarily less breast milk]. In most cases, the amount of breast milk returned to normal after a few days."* About 10% of the women said they had stopped breastfeeding. *The fact that they have stopped does not necessarily have to be because they have received the corona vaccine*". Out of 200 reports mentioned in the article, just 3 patients received Janssen vaccine, and most cases were reported following Pfizer vaccine (about 177)."*Based on the reports of decreased milk supply during breastfeeding after COVID-19 vaccination, a causal relationship cannot be ruled out and should be further investigated. This potential adverse reaction may create a substantial burden for lactating women. More knowledge is important for informing lactating women.*"

Use during pregnancy and while breastfeeding is classified as Missing Information in the core RMP (cRMP) for the Janssen COVID-19 vaccine, both a pregnancy registry (VAC31518COV4005) and an open-label phase 2 study in pregnant patients (VAC31518COV2004) are included in the PP. As also stated in the cRMP, "*Breastfeeding women were excluded from all clinical trials, except from Phase 3 trials COV3001 and COV3009. Up to the DLP of the EU-RMP that was part of the initial cMAA submission (22 January 2021), 128 breastfeeding women have received Ad26.COV2.S in trial COV3001, but no data are currently available from these trials in this subpopulation. [....] A small subset of participants within trial COV2004 will be followed up during breastfeeding to assess the transfer of antibodies via breast milk. [....] the safety profile of Ad26.COV2.S in breastfeeding women has not been established and the risk in this population has not yet been defined.*" The Pregnancy, Breastfeeding, and Fertility Section of the CCDS states, "*Safety data with TRADENAME when administered within 3 months before pregnancy as well as during pregnancy have shown no safety*

[16] https://www.uptodate.com/contents/acalculous-cholecystitis-clinical-manifestations-diagnosis-and-management

[17] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7456800/

concerns in the mother or child in over 500 reported pregnancies, with over 100 reported pregnancy outcomes" (see Section 16.3.5.1, Use During Pregnancy for a discussion of the interval data regarding pregnancy and lactation).

Merino D, Gerard AO, Van Obberghen EK, et al. COVID-19 Vaccine-Associated Transient Global Amnesia: A Disproportionality Analysis of the WHO Safety Database. *Front. Pharmacol.* 2022;13.

Abstract: COVID-19 spread rapidly, resulting in a global pandemic for which vaccines were quickly developed. As their safety continues to be monitored, cases of transient global amnesia (TGA) following mRNA vaccination with elasomeran have been reported. TGA is characterised by sudden onset of anterograde amnesia with preservation of other cognitive functions and resolution within 24 hours. We aimed to investigate the potential link of TGA with COVID-19 vaccines. We queried the WHO VigiBase for all reports of "Transient global amnesia", up to 06 December 2021. Disproportionality analysis relied on the Reporting Odds Ratio (ROR) with its 95% Confidence Interval (CI) and the Information Component (IC). A positive lower end of the 95% CI of the IC (IC025) is used to statistically detect a signal. Of all TGA cases, 289 were associated with a COVID-19 vaccine, representing the most frequent association. Tozinameran was mostly represented (147, 50.8%), followed by AZD1222 (69, 23.8%), elasomeran (60, 20.8%), and JNJ-78436735 (12, 4.2%). With an IC025 > 0, COVID-19 vaccines showed a significant ROR (5.1; 95%CI 4.4 to 6.0). Tozinameran reached the strongest ROR (4.6; 95%CI 3.9 to 5.0), followed by elasomeran (4.4; 95%CI 3.4 to 6.0), AZD1222 (3.8; 95%CI 3.0 to 5.0), and JNJ-78436735 (3.7; 95%CI 2.1 to 6.0). Our analysis of COVID-19 vaccines-related TGA reports shows significant disproportionality. Cerebrovascular, inflammatory, or migrainous mechanisms may underlie this association. Yet, numerous confounding factors cannot be tackled with this approach, and causality cannot be ascertained. The identification of this trigger of TGA may help the clinician in his etiological research.

MAH Comment: Review of WHO safety database (Vigibase) of all notified TGA cases for the period from 14 November 1967 to 06 December 2021 was conducted. A disproportionality analysis identified that of all TGA cases, COVID-19 vaccine represented the most frequent association. Twelve reports for Janssen vaccine (4.2%) were identified. According to disproportionality analysis, COVID-19 vaccines were characterised by the strongest ROR with the strongest ROR reported for the Pfizer vaccine (ROR 4.6; 95% CI 3.9 to 5.0), followed by Moderna (ROR 4.4; 95% CI 3.4 to 6.0), AstraZeneca (ROR 3.8; 95% CI 3.0 to 5.0) and Janssen vaccine (ROR 3.7; 95% CI 2.1 to 6.0). No detailed information on TGA cases at the individual level was available; hence, given the study limitations (reporting bias, under-reporting, coding heterogeneity, incomplete data) an association to vaccination cannot be ascertained. Taking into consideration other potential aetiologic factors and missing information on these reports, no safety signal was identified at this time.

Moro P, Olson C, Clark E, et al. Post-authorization surveillance of adverse events following COVID-19 vaccines in pregnant persons in the vaccine adverse event reporting system (VAERS), December 2020 to October 2021. *Vaccine.* 2022;40(24):3389-3394.

Background: Pregnant persons are at increased risk of severe illness from COVID-19 infection, including intensive care unit admission, mechanical ventilation, and death compared with non-pregnant persons of reproductive age. Limited data are available on the safety of COVID-19 vaccines administered during and around the time of pregnancy.

Objective: To evaluate and summarise reports to the VAERS, a national spontaneous reporting system, in pregnant persons who received a COVID-19 vaccine to assess for potential vaccine safety problems.

Method: We searched VAERS for US reports of AEs in pregnant persons who received a COVID-19 vaccine from 14 December 2020 to 31 October 2021. Clinicians reviewed reports and available medical records. Crude reporting rates for selected AEs were calculated, and disproportional reporting was assessed using data mining methods.

Results: VAERS received 3,462 reports of AEs in pregnant persons who received a COVID-19 vaccine; 1,831 (52.9%) after BNT162b2, 1,350 (38.9%) after mRNA-1273, and 275 (7.9%) after Ad26.COV2.S. Eight maternal deaths and 12 neonatal deaths were reported. Six-hundred twenty-one (17.9%) reports were serious. Pregnancy-specific outcomes included: 878 spontaneous abortions (<20 weeks), 101 episodes of vaginal bleeding, 76 preterm deliveries (<37 weeks), 62 stillbirths (≥20 weeks), and 33 outcomes with birth defects. Crude reporting rates for preterm deliveries and stillbirths, as well as maternal and neonatal mortality rates were below background rates from published sources. No disproportional reporting for any AE was observed.

Conclusion: Review of reports to VAERS following COVID-19 vaccines in pregnant persons did not identify any concerning patterns of maternal or infant-foetal outcomes.

MAH Comment: Out of 275 reports after Ad26.COV2.S vaccine 84 were pregnancy specific, including spontaneous abortions (n=55), vaginal bleeding (n=6), preterm delivery (n=3), stillbirths (n=4), placental abnormalities (n=4), preeclampsia/gestational hypertension (n=9), ectopic/molar pregnancy (n=2), and other (n=5). Besides these the authors also presented infant specific cases (n=4) such as neonatal deaths (n=2), infant in intensive care unit (diverse abnormalities) (n=1), other infant conditions (n=1). The authors noted that, "*No disproportional reporting for any AE was observed*" and "*Using published [...] vaccination coverage data for COVID-19 vaccines, we estimated that the crude reporting rate of stillbirths is 17.3 reports per 100,000 stillbirths and live births, for preterm deliveries 21.4 reports per 100,000 live births, for maternal deaths 2.3 per 100,000 live births, and for neonatal deaths 3.4 per 100,000 live births [...] All crude reporting rates were below published background rates for these conditions*". No new safety signal was identified.

Use during pregnancy is classified as Missing Information in the RMP for the Janssen COVID-19 vaccine, both a pregnancy registry (VAC31518COV4005) and an open-label phase 2 study in pregnant patients (VAC31518COV2004) are included in the EU RMP and Pharmacovigilance Plan (PVP). The Pregnancy, Breastfeeding, and Fertility Section of the CCDS states, "*Safety data with TRADENAME when administered within 3 months before pregnancy as well as during pregnancy have shown no safety concerns in the mother or child in over 500 reported pregnancies, with over 100 reported pregnancy outcomes*" (see to Section 16.3.5.1, Use During Pregnancy for a discussion of the interval data regarding pregnancy).

Nyankerh CNA, Boateng AK, Appah M. Ocular Complications after COVID-19 Vaccination, Vaccine Adverse Event Reporting System. *Vaccines*. 2022;10(6).

Abstract: In December 2020, the US FDA licensed COVID-19 vaccines for emergency use authorisation. We investigated the ocular AE reports in patients reported to the VAERS following vaccination against COVID-19. We searched the VAERS database for US reports among persons who received COVID-19 vaccines between December 2020 and December 2021. Our goal was to analyse and quantify the ocular AEs submitted to VAERS to provide clinicians and researchers with a broader view of these ocular side effects. During the analysis period, VAERS received 55,313 AE reports and, after data cleaning, 6,688 reports met the inclusion criteria. Note that 2,229 (33.33%) AEs were classified as cases of eyelid swelling, ocular hyperemia, and conjunctivitis; 1,785 (26.69%) as blurred vision, and 1,322 (19.77%) as visual impairment. Females accounted for 73.8% of AE reports and the age group between 40 and 59 years had the most frequent AEs. A higher proportion of these AEs reported to VAERS was linked with the Janssen and Moderna COVID-19 vaccines. At the time of vaccination, a high proportion of patients reported conditions like allergies, hypertension, diabetes,

thyroid disease, vascular, and other autoimmune diseases. A review of these data suggests a possible association between COVID-19 vaccines and ocular AEs. Physicians are cautioned not only to be aware of this potential problem, but to check any underlying patient conditions, and to carefully document in VAERS within a few weeks of vaccination. Future COVID-19 vaccine safety studies in healthy subjects would help clarify the vaccine's safety profile.

MAH Comment: The study aimed to "*analyze and quantify the ocular adverse events submitted to VAERS to provide clinicians and researchers with a broader view of these ocular side effects*." The period covered was December 2020 to December 2021. Out of the patients who had ocular complications, "*3346 (50%) received the Pfizer-BioNTech vaccine, 2552 (38.2%) received the Moderna vaccine and 790 (11.8%) received the Janssen vaccine*." According to the study authors, "*To test the null hypothesis that the vaccines administered were associated with ocular adverse events, [they] performed a chi-square test of association. Surprisingly, the Janssen and Moderna vaccines were mostly associated with the reported ocular adverse events in VAERS.*" The authors stated that, "*[...] the Janssen vaccine had a significantly higher proportion of adverse events for all cases except for eyelid swelling, ocular hyperemia, conjunctivitis, which had a higher proportion of adverse events associated with the Moderna vaccine."* Worth mentioning that, "*These ocular events have also been reported in patients who have suffered the COVID-19 disease, which may suggest a shared common pathway of the ocular complications associated with the COVID-19 disease and post-vaccination events.*" Nevertheless, the authors also emphasised that "*since [they] did not have data showing the number of doses or boosters per vaccine type administered to each patient, trying to establish a cause-effect relationship will be implausible. Also, since VAERS does not include an unvaccinated group, [they] could not calculate rates nor determine if the vaccines themselves are associated with an increased risk of adverse events.*" Taking into consideration the study limitations (passive, biased, and stimulated reporting, missing information on cases, affected quality and accuracy of the information, etc), there is no new safety signal identified at this time.

Priluck A, Arevalo J, Pandit R. Ischemic retinal events after COVID-19 vaccination. *Am. J. Ophthalmol. Case Rep*. 2022;26.

Purpose: We report 2 cases of ischaemic retinal events occurring soon after administration of the Moderna and Johnson & Johnson/Janssen COVID-19 vaccines. To our knowledge, these are the first reports of isolated ischaemic retinal events occurring after COVID-19 vaccination.

Observations: A 57-year-old female had new onset floaters of the left eye within days of her second Moderna COVID-19 vaccination, which progressively worsened prompting her to present for evaluation. The patient was diagnosed with a branch retinal vein occlusion in the left eye. A 20-year-old female presented with persistent central scotomata in both eyes, which she first noticed 2 days after her Johnson & Johnson/Jannsen COVID-19 vaccination. She was diagnosed with acute macular neuroretinopathy of both eyes.

Conclusion: The potential side effects of COVID-19 vaccines are still being established; however, there has been concern over pro-thrombotic events with these vaccines, with most concerns directed toward the Johnson & Johnson vaccine. We observed likely transient pro-thrombotic retinal milieu in patients who received these vaccines though it remains unclear whether there is a shared mechanism between systemic response to the COVID-19 spike protein and the highly pro-thrombotic state seen in COVID-19 infections. In the case of our patients, we postulate their immunologic responses to the vaccines and possibly a resultant pro-thrombotic state may have precipitated their ischaemic retinal events. We thus recommend that patients with ocular symptoms after COVID-19 vaccination undergo comprehensive ophthalmologic evaluation.

MAH Comment: Acute macular neuroretinopathy presents predominantly in females in their twenties, is bilateral in over half of patients, and while the mechanism(s) are poorly understood, has been associated with multiple potential risk factors, including in 1 series with oral contraceptives in

35.6% of patients (Bhavsar KV 2016). Both cases present acute macular neuroretinopathy after receiving COVID-19 vaccination: in the first case after the second dose of Moderna and in the second case after the Janssen COVID-19 vaccine. In the second case, the patient reported using norgestimate-ethinyl estradiol, which is an oral contraceptive. Use of oral contraceptives is a known risk factor for the development of acute macular neuroretinopathy (Bhavsar KV 2016).

According to the PBRER covering the period of 25 August 2021 to 24 February 2022, "*As requested in EMEA/H/C/005737/MEA/014.7: "[...] a cumulative review of acute macular neuroretinopathy (AMN) in subjects having been vaccinated with the COVID-19 vaccine Janssen*" was conducted. Based on the MAH conclusion, "*A causal relationship between AMN and Ad26.COV2.S could not be established based on the totality of data analyzed including a cumulative review of cases reported in association with Ad26.COV2.S vaccine, the literature, and the O/E analysis. The Company will continue to monitor this event through routine pharmacovigilance activities*."

Based on the presented cases and both the known and unknown characteristics of this disease state, no new safety information is detected at this time.

Rodriguez Quejada L, Toro Wills MF, Martinez-Avila MC, Patino-Aldana AF. Menstrual cycle disturbances after COVID-19 vaccination. *Womens health.* 2022;18: 17455057221109375.

Introduction: After COVID-19 vaccination, women of reproductive age reported changes in their menstrual cycle.

Materials and Methods: A retrospective study was carried out after a survey on social networks that included women aged 18 to 41 years with normal cycles according to International Federation of Gynaecology and Obstetrics and who were vaccinated (complete schedule for 2 doses, except J&J/Janssen or incomplete with a single dose). Women with the following conditions were excluded: pregnant or lactating women; history of diseases that cause menstrual irregularities or early menopause: anorexia, bulimia, polycystic ovary syndrome, hypothyroidism, obesity, or low weight; hysterectomised or oophorectomised patients; and high performance athletes.

Results: Overall, 950 women completed the survey between July and September 2021. In total, 408 women met the inclusion criteria, and 184 reported the following characteristics: frequency (normal 43.47%, infrequent 25%, and frequent 31.53%), regularity (regular 51.08%, irregular 42.93%, and absent/amenorrhoea 5.97%), duration (normal 65.21%, prolonged 26.08%, absent/amenorrhoea 8.69%), and volume (heavy 41.84%, light 20.65%, and absent/amenorrhoea 6.52%).

Conclusions: SARS-CoV-2 infection and COVID-19 vaccination can influence the menstrual cycle and cause alterations.

MAH Comment: The retrospective study results based on a survey of a women population aged 18 to 41 years identified per inclusion/exclusion criteria revealed that 184 women reported alterations in the menstrual cycle. "*Of the 184 women who reported alterations in the menstrual cycle, [....] Overall, 150 (81.5%) women had a complete vaccination schedule, mostly with Sinovac (n=53; Pfizer (n=51), J&J/Janssen (n=33), others (n=19), Modern (n=15), AstraZeneca (n=13))*." Janssen vaccine was identified as the one with more women in the subgroup who reported irregular cycles (n=19) than normal (58% versus 42%). In addition, 18 women in the Janssen vaccine subgroup reported heavy cycles in the post-vaccination period. Also, 70% of women in the Janssen vaccine subgroup reported a change in quality of life. According to the authors, "*A plausible theory for [menstrual blood volume alteration] is extrapolated from the pathophysiology of patients with abnormal uterine bleeding due to increased volume. In these patients, a marked expression of macrophages and endometrial leukocytes capable of secreting powerful vasodilators is observed, explaining the increased volume of bleeding in patients*."

Based on the information available then in the Company Signal Tracking System, "*On 23 Feb 2022 a signal was identified for Menstrual cycle and uterine bleeding disorders and Postmenopausal haemorrhage with the use of COVID-19 VACCINE AD26.COV2.S based on an aggregate review of post marketing data reported in the Company database and the Food and Drug Administration Vaccine Adverse Event Reporting System database.*" The rationale for creating the signal was "*[...] the impact of the events on patient quality of life and the fact that is a safety topic with regulatory interest.*" However, following the review of data from the Global Safety database and the Food and Drug Administration (FDA) Vaccine Adverse Event Reporting System (VAERS), menstrual cycle and uterine bleeding disorders and post-menopausal haemorrhage safety signal was not validated due to lack of sufficient evidence to establish an association.

The current study has several limitations (study design, information and selection biases). Given the study limitations and limited information, no safety signal was identified at this time.

Sa S, Lee CW, Shim SR, et al. The Safety of mRNA-1273, BNT162b2 and JNJ-78436735 COVID-19 Vaccines: Safety Monitoring for Adverse Events Using Real-World Data. *Vaccine*. 2022;10(2):320.

Abstract: Two mRNA COVID-19 vaccines (mRNA-1273, Moderna; and BNT162b2, Pfizer-BioNTech) and 1 viral vector vaccine (JNJ-78436735, Janssen/Johnson and Johnson) are authorised in the US to hinder COVID-19 infections. We analysed severe and common AEs in response to COVID-19 vaccines using real-world, VAERS data. From 14 December 2020 to 30 September 2021, 481,172 (50.7 ± 17.5 years, males 27.89%, 12.35 per 100,000 people) individuals reported AEs. The median time to severe AEs was 2 days after injection. The risk of severe AEs following the 1 viral vector vaccine (OR = 1.044, 95% CI = 1.005 to 1.086) was significantly higher than that after the 2 mRNA vaccines, and the risk among males (OR = 1.374, 95% CI = 1.342 to 1.406) was higher than among females, except for anaphylaxis. For common AEs, however, the risk to males (OR = 0.621, 95% CI = 0.612 to 0.63) was lower than to females. In conclusion, we provided medical insight and clinical guidance about vaccine types by characterising AEs using real-world data. In particular, COVID-19 mRNA vaccines are safer than viral vector vaccines with regard to coagulation disorders, whereas inflammation-related AEs are lower in the viral vaccine. The risk-benefit ratio of vaccines should be carefully considered, and close monitoring and management of severe AEs is needed.

MAH Comment: The authors, "*selected 25 severe AEs, one of which was death, on the advice of a focus group of 3 clinical experts*" which are listed in table S2 of the article. The authors stated, "*Following mRNA 1273, BNT162b2, and JNJ-78436735 administration, death was reported in 2286, 2005, and 447 cases, respectively. Although JNJ-78436735 reported fewer cases, the incidence per 100,000 people was 2 to 3 times higher than that after the mRNA vaccines*" and for death "*the odds ratio of the viral vector vaccine to the mRNA vaccines was 1.901 (CI=1.713-2.111) (Table S5).*" Regarding reported associations with death across all 3 vaccines, the authors state, "*multivariate logistic regression analysis for death after adjusting for sex (reference: female), age, symptom onset (number of days), and vaccine type (reference: BNT162b2) with severe AEs as covariates revealed that acute respiratory distress syndrome (OR=20.510, CI=12.620-33.332, p<0.001), haemorrhagic stroke (OR=9.965, CI=6.406-15.499, p<0.001), and acute myocardial infarction (OR=3.872, CI=2.794 5.366, p<0.001) were most significantly associated with post-vaccination mortality.*" Regarding event associations with death, the authors' Table 2 reports incidence rates per 100,000 population/study period for the Moderna, Pfizer, and Janssen vaccines, respectively, as follows: acute respiratory distress syndrome, 0.03, 0.02, and 0.11; haemorrhagic stroke, 0.05, 0.04, 0.24; acute myocardial infarction, 0.15, 0.13, and 0.29. Known limitations from the study were noted by the authors, including the voluntary and fragmentary nature of reporting from VAERS.

Regarding the events associated with death with the Janssen COVID-19 vaccine, the authors referred to cases of acute respiratory distress syndrome associated with Janssen COVID-19 vaccine likely related to cases of COVID-19 infection reported prior to the implementation of the booster vaccination with Ad26.COV2.S vaccine (the study used data from US FDA VAERS database covering the period from 14 December 2020 to 30 September 2021). The higher incidence of events of haemorrhagic stroke are likely related to the events of thrombosis and thrombocytopenia which is now an established adverse reaction associated with Ad26.COV2.S vaccine. Another higher incidence was identified with cases of GBS also considered as ADR in the CCDS of the Ad26.COV2.S vaccine. The event of acute myocardial infarction is closely monitored by the Company as an adverse event of special interest (AESI), in addition, the Company conducted a cumulative review of events of coronary artery disease (CAD) including myocardial infarction to address a request from PRAC (see Section 16, Signal and Risk Evaluation). The analysis of all available data, the weight of cumulative evidence is insufficient to support a causal association between CAD (including acute myocardial infarction [AMI]) and the Ad26.COV2.S vaccine. Key factors supporting this conclusion include lack of established biological plausibility, no increased risk observed from review of a large clinical trial dataset, and insufficient evidence from the biomedical literature, clinical trials, literature and aggregate post-marketing spontaneous reports and as well as RWE to support an association between the development of CAD (including AMI) and Ad26.COV2.S. The safety signal was not confirmed. The review of this study results did not identify any new safety information.

Woodcock R. Bartels L. Preliminary Evidence of a Link between COVID-19 Vaccines and Otologic Symptoms. *MedRxiv*. 2022.

Hypothesis: This study investigates whether US Centers for Disease Control and Prevention VAERS data suggest an association between vertigo, tinnitus, hearing loss, Bell's palsy and the COVID-19 vaccines administered in the US.

Background: Published case reports suggest a possible association between various otologic symptoms and the COVID-19 vaccines, but the only published analysis of VAERS data, which did not account for underreporting of late-appearing AEs, found no association between hearing loss and the vaccines.

Method: The incidence in VAERS of vertigo, tinnitus, hearing loss, and Bell's palsy associated with COVID-19 vaccinations administered between 14 December 2020 and 07 June 2021 was compared with published rates for the general population. To account for underreporting of late-appearing AEs, incidences were calculated using only the initial part of the observation period, during which reported events spike above expected events.

Results: The COVID-19 vaccines were associated with statistically significant increases in the incidence of vertigo, tinnitus, hearing loss, and Bell's palsy of 1,877, 50, 12, and 14 cases per 100,000, respectively. In relation to the mRNA-1273 or BNT162b2 vaccines, the Ad26.COV2.S vaccine was associated with a statistically significant excess incidence of vertigo, tinnitus, and hearing loss of at least 723, 57, and 55 cases per 100,000, respectively.

Conclusion: These results suggest an association between the COVID-19 vaccines and vertigo, tinnitus, hearing loss, and Bell's palsy. They also suggest that, with respect to vertigo, tinnitus, and hearing loss, the association is relatively strong for the Ad26.COV2.S vaccine.

MAH Comment: The authors present that the incidence of tinnitus, hearing loss, vertigo is significantly higher after Ad.26.COV2.S use. Three out of the 4 mentioned events (tinnitus, vertigo, and Bell's palsy) are listed in the CCDS's Adverse Reactions section.

The authors of this article do not provide sufficient information regarding hearing loss. The observation lacks data about the type of hearing loss (sensorineural, conductive, mixed loss), cases' full auditory history, and examination performed (Weber, Rinne tests, pneumoscopy, pure tone, air,

and bone conduction testing, etc.). No new safety information is detected at this time; refer to Section 16.3.6.3.5, Sensorineural Hearing Loss for a discussion of the interval data regarding hearing loss.

11.2. Class Effect Literature

Hertel M, Schmidt-Westhausen AM, Wendy S, et al. Onset of Oral Lichenoid Lesions and Oral Lichen Planus Following COVID-19 Vaccination: A Retrospective Analysis of about 300,000 Vaccinated Patients. Vaccines (Basel). 2022;10(3):480.

Introduction: Onset of oral lichenoid lesions (OLL) or oral lichen planus (OLP) can be rare adverse reactions to vaccines. Recently, the first solitary cases were reported after COVID-19 vaccination. The aim of the present study was to assess if an increased frequency of OLL/OLP can be found after COVID-19 vaccination within a large real-world cohort. It was assumed that the incidence of OLL/OLP was significantly higher in subjects who received COVID-19 vaccine (cohort I) compared to individuals who were not vaccinated (cohort II).

Methods: Initial cohorts of 274,481 vaccinated and 9,429,892 not vaccinated patients were retrieved from the TriNetX database (TriNetX, Cambridge, Massachusetts, US), and matched for age, gender and the frequency of use of non-steroidal anti-inflammatory drugs, beta blockers, and angiotensin-converting enzyme inhibitors.

Results: After matching each cohort, we accounted for 217,863 patients. Among cohort I, 146 individuals experienced OLL/OLP within 6 days after COVID-19 vaccination (88 and 58 patients had received mRNA and adenovirus vector-based vaccines), whereas in cohort II, 59 patients were newly diagnosed with OLL/OLP within 6 days after having visited the clinic for any other reason. The risk of developing OLL/OLP was calculated as 0.067% vs. 0.027%, for cohorts I and II, whereby the risk difference was highly significant ($p < 0.001$; log-rank test). RR and OR were 2.475 (95% CI = 1.829; 3.348) and 2.476 (95% CI = 1.830; 3.350), respectively.

Conclusion: The hypothesis was confirmed. Accordingly, the obtained results suggest that the onset of OLL/OLP is a rare ADR to COVID-19 vaccines, especially to mRNA vaccines. Thus far, it remains unknown if specific components of the formulations cause a type IV hypersensitive reaction corresponding to OLL, or if the immune response post vaccination triggers a T cell-driven autoimmune reaction directed against the basal layer of keratinocytes of the oral mucosa in terms of OLP. Although OLL and OLP are both classified as premalignant lesions, spontaneous remission may be expected over time, at least in the case of OLL. Therefore, the presented findings should not place any limitation toward the use of COVID-19-vaccines in broad levels of the population

MAH Comment: Eighty-eight and 58 subjects who experienced OLL/OLP had received mRNA and adenovirus vector-based vaccines. As stated by the authors, "*Despite the matching process, a difference in the proportion of the subjects using NSAIDs remained, [which means] that the distribution difference in the frequency of the use of NSAIDs between both cohorts cannot be eliminated.*" They also pointed out that "*the presented analysis found cases of newly diagnosed OLL/OLP in which adenovirus vectors had been administered as well, [hence it could] be carefully assumed that the presentation of the viral spike protein to the hosts immune system might play a role in the pathological mechanism, causing OLL/OLP following COVID-19 vaccination.*" Both OLL and OLP "are classified as premalignant lesions with an augmented risk of transformation into an oral squamous cell carcinoma", however, the literature states that the magnitude of the risk of malignant transformation of OLP to oral squamous cell carcinoma is unclear.[18] The prevalence of OLP is 1 to

[18] https://www.uptodate.com/contents/oral-lichen-planus-management-and-prognosis

3 % in the general population[19] and an incidence is in the range of ~60 to 190 per 100,000 person-years (Nagao 2005). The incidence in general population of OLL is unknown. Taking into consideration the limitations of the study, as well as lack of differential diagnosis and missing information on cases, there is no new safety signal identified at this time.

Ma Y, Xu G. New-Onset IgA nephropathy Following COVID-19 Vaccination. QJM: An International Journal of Medicine. 2022.

Abstract: COVID-19 pandemic, caused by SARS-CoV-2, has caused significant economic and health damage worldwide. Rapid vaccination is 1 of the key strategies to curb severe illness and death due to SARS-CoV-2 infection. Hundreds of millions of people worldwide have received various COVID-19 vaccines, including mRNA vaccines, inactivated vaccines and adenovirus-vectored vaccines, but the side effects and efficacy of most vaccines have not been extensively studied. Recently, there have been increasing reports of immunoglobulin A nephropathy (IgAN) after COVID-19 vaccination, however, whether their relationship is causal or coincidental remains to be verified. Here, we summarise the latest clinical evidence of IgAN diagnosed by renal biopsy associated with the COVID-19 vaccine published by 10 July 2022 with the largest sample size and propose a hypothesis for the pathogenesis between them. At the same time, the new opportunity presented by COVID-19 vaccine allows us to explore the mechanism of IgAN recurrence for the first time. Indeed, we recognise that large-scale COVID-19 vaccination has enormous benefits in preventing COVID-19 morbidity and mortality. The purpose of this review is to help guide the clinical assessment and management of IgA nephropathy post-COVID-19 vaccination and to enrich the 'multi-hit' theory of IgA nephropathy.

MAH Comment: The article presents 48 cases of IgA nephropathy from the literature. Patients received Pfizer, Moderna, and AstraZeneca vaccines. The authors state, "*the patients [they] reported are from a single case study, and there is only a temporal association between symptom onset and COVID-19 vaccination in IgAN patients, and [they] are unable to infer a causal relationship between vaccine and IgAN*". As per the Summary Safety Report (SSR) covering the period from 16 January 2022 through 15 March 2022, upon request from the WHO Uppsala monitoring centre on 22 February 2022 safety signal was opened and "*comprehensive search of clinical and post marketing database for adverse event reports [was performed]. [...] Based on the review of evidence from cases from interventional clinical studies and post-marketing surveillance data, there [was] no evidence of causal association between the event of IgA nephropathy and vaccination with Ad26.COV2. S. vaccine*". The presented reference does not provide additional evidence to the completed above described comprehensive review. No new safety information is detected at this time.

12. OTHER PERIODIC REPORTS

This section is not applicable as no other COVID-19 Vaccine PBRERs concerning Ad26.COV2.S have been prepared.

13. LACK OF EFFICACY IN CONTROLLED CLINICAL TRIALS

Although protection with a single-dose of Ad26.COV2.S in adults ≥18 years of age, including in adults ≥60 years of age against severe/critical COVID-19, including hospitalisations and deaths related to COVID-19, continued to be observed over time, across age groups, comorbidities, countries, regions, and emerging SARS-CoV-2 variants, including variants of concern/variants of interest (variants of concerns (VOC)/VOIs), there was a trend towards a decreased protection

[19] https://www.uptodate.com/contents/oral-lichen-planus-pathogenesis-clinical-features-and-diagnosis

against moderate to severe/critical COVID-19 over time. Protection against moderate to severe/critical COVID-19 varied by (newly) emerging SARS-CoV-2 variants, including VOCs/VOIs, throughout the trial, and this potentially contributes to the observed decrease, although waning protection of Ad26.COV2.S cannot be excluded. Efficacy results from the primary analysis of ongoing Phase 3 trial VAC31518COV3009, in which an Ad26.COV2.S booster dose was administered 2 months after the first vaccination, suggest that protection against moderate to severe/critical COVID-19 (including against SARS-CoV-2 VOC) and severe/critical COVID-19 increased after a homologous booster dose administered 2 months after the single-dose primary vaccination.

When considering the VE against SARS-CoV-2 variants, including VOCs/VOIs, observed in Trial VAC31518COV3001, caution is needed when interpreting data where there were (too) few COVID-19 cases and/or CIs were wide. Differences were observed in protection against moderate to severe/critical COVID-19. No reduction in VE estimates compared to that of the reference strain (VE estimate [95% CI]: 58.2% [34.96; 73.72] at least 28 days after vaccination) for the Alpha VOC and other variants was observed, while the VE estimates for the Delta, Gamma VOCs, Mu, Lambda VOIs were reduced (<36%). The VE estimate (95% CI) for the Beta VOC, at least 28 days after vaccination was 51.9% (19.06; 72.19). For severe/critical COVID-19, the VE estimates were 63% to 91% across variants with sufficient COVID-19 cases, such as Beta, Gamma VOCs, and Lambda, Mu VOIs. In summary, in the double-blind randomised placebo-controlled trial, a single-dose of Ad26.COV2.S provided at least 6 months of protection against severe/critical disease, hospitalisation, and death, with varying degrees of protection against symptomatic disease depending on the variant.

Since the clinical trial VE estimates are below 100%, particularly for mild and moderate disease, breakthrough cases in vaccinated individuals are expected to occur.

Altogether, the totality of data allows us to conclude that vaccination with Ad26.COV2.S remains efficacious against severe/critical COVID-19, including hospitalisations and deaths related to COVID-19, including against some variants. While the analysis of Delta cases from clinical trials remains inconclusive, multiple sources of evidence confirm vaccine effectiveness against observed COVID-19 and COVID-19-related hospitalisation related to the Delta and Omicron VOC in a real-world setting.

14. LATE-BREAKING INFORMATION

Thrombocytopenia and Single Organ Cutaneous Vasculitis

On 31 August 2022, both thrombocytopenia and single organ cutaneous vasculitis were identified to have an association with Ad26.COV2.S from the review of the VAC4EU COVID vaccine safety monitoring system. Both events are already listed as adverse reactions following earlier assessments from the EMA PRAC as immune thrombocytopenia and cutaneous small vessel vasculitis respectively. After the data lock point, the Company opened a safety signal based on the disproportionate reporting of vasculitis, particularly cutaneous vasculitis. The evaluation of this signal is ongoing and will be presented in the next PBRER.

15. OVERVIEW OF SIGNALS: NEW, ONGOING, OR CLOSED

15.1. Ongoing Signals

There were no signals that were undergoing evaluation at DLD of this report.

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

15.2.1. Glomerulonephritis and Nephrotic Syndrome

Request: According to the PRAC Final Assessment Report (FAR) (PRAC AR 2022) for the Ad26.COV2.S PBRER (EMEA/H/C/PSUSA/00010916/202202) received on 29 September 2022, the MAH was requested to address the following in the current report:

"*A cumulative review of glomerulonephritis and nephrotic syndrome should be submitted. This should include a search conducted at the level of HLT "glomerulonephritis and nephrotic syndrome". Furthermore, the MAH should provide relevant data from the literature and clinical trials. The MAH should provide causality assessments, and based on these data, discuss the need for updating the product information and/or risk management plan, and submit proposals as required.*"

MAH Conclusion: The Company conducted a comprehensive cumulative review of glomerulonephritis and nephrotic syndrome per the above PRAC request. Based on the totality of cumulative post-marketing and clinical trial data and comprehensive literature review, there is insufficient information to suggest an association between Ad26.COV2.S and the occurrence of glomerulonephritis and nephrotic syndrome.

Supporting conclusions from this report were:

- no clear mechanism of action (MOA) has been established in association with any vaccine although possible MOA have been suggested.
- no cases occurred in the Ad26.COV2.S group during the double-blind phase of the pooled analysis. For all ongoing Ad26.COV2.S clinical trials, covering the period beyond the double-blind pooled analysis, there were 3 participants who experienced a "glomerulonephritis and nephrotic syndrome" following Ad26.COV2.S vaccination during the open-label phase. All 3 cases were considered 'not related' by the investigator and had an onset beyond day 90 post-vaccination.
- insufficient evidence regarding an association role of the Ad26.COV2.S vaccine and glomerulonephritis and nephrotic syndrome based on the review of post-marketing data.
- both disproportionality datamining and RWE rapid cycle analysis were not conclusive because data was not consistent across data sources.
- O/E ratio <1 across the broad analysis, inconsistent pattern was identified for the sensitivity and restricted analysis in terms of age, gender and region.

The Company will continue to monitor glomerulonephritis and nephrotic syndrome via routine pharmacovigilance activities.

Additional information on this analysis can be found in Appendix 9.1 and also in Section 2.1 of the Response document titled: Response to the PRAC Rapporteur's Preliminary Assessment Report: Periodic Safety Update Report (Reporting Period: 25 August 2021 to 24 February 2022) JCOVDEN Procedure Number: EMEA/H/C/PSUSA/00010916/202202 (dated 26 August 2022).

15.2.2. Severe Cutaneous Adverse Reactions

On 30 May 2022, the Company received a request from the Uppsala Monitoring Centre (UMC) to provide a comment on their observed signal (based on WHO VigiBase data) on severe cutaneous adverse reactions (SCAR). This topic had been discussed in detail in the previous PBRER (DLD of 24 February 2022), where the Company concluded there was insufficient evidence to associate SCAR or Erythema multiforme to Ad26.COV2.S. The Company submitted the results of this evaluation to UMC, this topic is considered closed and refuted.

In the PRAC FAR (EMEA/H/C/PSUSA/00010916/202202), for the Ad26.COV2.S PBRER dated 25 August 2021 to 24 February 2022, PRAC indicated that routine monitoring is sufficient.

15.2.3. Neuralgic Amyotrophy

Request: According to the PRAC FAR (PRAC AR 2022) for the Ad26.COV2.S PBRER (EMEA/H/C/PSUSA/00010916/202202) received on 29 September 2022, the MAH was requested to address the following in the current report:

"Neuralgic Amyotrophy: A small number of cases of neuralgic amyotrophy has been identified cumulatively. There is currently insufficient support for an update to the product information. An updated cumulative review, where new cases are clearly marked should be provided in the next PSUR."

Conclusion: Based on the totality of data reviewed from the Company global safety database there is insufficient evidence to establish a causal role of the Ad26.COV2.S vaccine in the occurrence of neuralgic amyotrophy (NA). Although the temporal relationships of the reported events to the vaccine in the 3 cases identified indicate that a causal relationship to the vaccine at individual case level is possible, diagnostic criteria specific to NA were not consistently demonstrated in the cases overall. No change to the product label is warranted.

Key factors to support this conclusion include:

- low number of cases reported cumulatively through 24 August 2022 (n=29) following a total of 52,684,577 doses of Ad26.COV2.S administered worldwide since launch.
- none of the 4 serious cases identified within the reporting period met the van Alfen 2015 diagnostic criteria for definitive or probable NA. However, 1 case met one of the 4 van Alfen diagnostic criteria and thus was assessed as possibly related.
- many of the cases contained limited information regarding relevant clinical data including supportive diagnostic testing, clinical course, concomitant medications/vaccinations, concurrent conditions/relevant medical history, duration of the event, and treatment; thus, precluding a thorough medical assessment.

This topic will continue to be monitored via routine pharmacovigilance activities. Additional information on this analysis can be found in Appendix 9.2.

15.2.4. Vasculitis

Request: According to the PRAC FAR (PRAC AR 2022) for the Ad26.COV2.S PBRER (EMEA/H/C/PSUSA/00010916/202202) received on 29 September 2022, the MAH was requested to address the following in the current report:

"*In the last SSR, (EMEA/H/C/005737/MEA/014.9), a request to provide continued detailed presentation of vasculitis cases, particularly those with systemic manifestations, was made for the next PSUR. The MAH will include address this in the next PSUR (DLP 24 August 2022). This is endorsed.*"

Conclusion: Following the review of both cumulative and interval reporting data, no changes are currently warranted to the prescribing information. The Company will continue to closely monitor cases of vasculitis, especially cases of small vessel vasculitis with systemic manifestations, and cases with medium- and large-vessel vasculitis.

Additional information on this analysis can be found in Appendix 9.3.

15.2.5. Thrombosis with Thrombocytopenia Syndrome

Request: According to the PRAC FAR (PRAC AR 2022) for the Ad26.COV2.S PBRER (EMEA/H/C/PSUSA/00010916/202202) received on 29 September 2022, the MAH was requested to address the following in the current report:

"*Given the removal lot XD955 in April 2022, and concerns from one member state of more reports of suspected ADRs for this batch than expected, and particularly in relation to TTS, the MAH should provide a summary of number of reported TTS cases, per specific batch number. The concerns that some quality problem with this batch could be involved in development of serious ADRs should also be addressed.*"

Post-marketing

Methods

The methodology is described in Section 16.3.1.1, Thrombosis with Thrombocytopenia Syndrome and in Appendix 5, List of Search Criteria for PBRER Sections. For this response, cases reporting at least 1 serious Preferred Term and a batch number were reviewed.

Results

Cumulatively, there were 227 primary dose cases received from post-marketing sources (including spontaneous and solicited cases) that reported at least 1 thromboembolic event and thrombocytopenia or decreased platelet count. An overview of the cumulative cases is presented in Section 16.3.1.1, Thrombosis with Thrombocytopenia Syndrome. The estimated cumulative

exposure numbers from marketing experience for distributed and administered doses by region are provided in Section 5.2, Cumulative and Interval Patient Exposure From Marketing Experience.

Of these, 108 cases did not report any batch number. The remaining 119 cases reported a batch number, and these are tabulated in Appendix 9.4.1, which includes patient demographics, serious events, outcomes per case, and diagnostic criteria (BC/CDC/PRAC).

In descending order, the batch numbers were: XD975 (n=8); 1808609, 1805020, 1805029 and 04321A (n=6 each); 1802070 and 1805022 (n=5 each); 1805025, 205A21A and 201A21A (n=4 each); 1808980, 042A21A, 21C13-05, 202A21A, XD974, XD985, 041A21A, 206A21A, 1805018, and 204A21A (n=3 each); 21C10-01, XE389, 21C17-04, 209A21A, 210A21A, XE423 (n=2 each); and 1 each for T306275, 1082068, 1802072, 203A21A, ACA5775, 211D21A, 1802068, 204B21A, 1808982, 21C11-01, 21C19-01, 21C11-03, 21C13-02, XD955, 1820095, 1805031, XE395, XD986, 1808978, XE393, 21C17-01, 21C14-03, 21C16-03.

Most cases were reported from the US (n=74) and Germany (n=11). Cases reported several events, and the more frequently reported events were cerebral venous sinus thrombosis, pulmonary embolism, deep vein thrombosis and/or thrombocytopenia and platelet count decreased. Of note, only 7 cases reported the PT Thrombosis with thrombocytopenia syndrome. The outcome for most cases was not reported or not resolved. There were no trends regarding the diagnostic criteria.

There were 18 cases with a fatal outcome. The cases regarding the 13 females (39- to 79-years- old) were from the US (n=10; batch 1802070, 1805022, 1805025, 1805020, 1805029), Spain (n=2; batch 21C19-01 and XE423) and France (n=1; batch 21C14-03). In cases regarding the 4 males (27- to 66- years old) were from Germany (n=2; batches XD974, XE395), and 1 each for Spain (batch 21C17-04) and US (batch 041A21A). There was 1 case from Poland in a 43-year-old patient (sex not reported) and the batch number was XE423. The CIOMS II LL are provided in Appendix 9.4.2.

Regarding batch number XD955, there was only 1 case which concerned a 42-year-old male who experienced the serious events of deep vein thrombosis in the lower left limb, embolism (also noted as pulmonary embolism) and thrombocytopenia 42 days after receiving the Ad26.COV2.S vaccine. The patient was hospitalised for an unspecified duration and treatment details were not provided. There was no information regarding the patient's past medical history or concurrent conditions or concomitant medications. The outcome for each event was not resolved. *(BC 5, CDC Neither [Non-tier 1/2)], PRAC Possible)*.

Conclusion

Upon review of post-marketing cases reporting a batch number and at least a 1 serious event, the batch analysis did not reveal quality concerns that could be linked to serious adverse reactions, including TTS.

15.3. Use With Concomitant Vaccination

Introduction

Use with concomitant vaccination is included within the PBRER in line with the GVP Module on Vaccines (Product- or Population-Specific Considerations I: Vaccines for prophylaxis against infectious diseases). This concerns a review of data for a potential safety issue after a subject receives a non-COVID-19 vaccine on the same day as Ad26.COV2.S.

A mixed schedule is defined as the administration of different vaccine types against COVID-19 on different dates. Cases reporting the use of heterologous boosters (mixed schedules) relevant to risks will be discussed in Section 16.3, Evaluation to Risks and New Information and relevant to specific AESI will be discussed under the relevant AESI subsection within Section 16.3.6, Adverse Event of Special Interest.

Trial VAC31518COV3005 is an ongoing randomised, double-blind, Phase 3 Study to evaluate the safety, reactogenicity, and immunogenicity of the simultaneous administration of Ad26.COV2.S and the influenza vaccines in healthy adults 18 years of age and older. There were no safety concerns identified from this trial during the reporting period.

Methods

The Company global safety database was searched for medically confirmed and medically unconfirmed cases received during this reporting period and cumulatively which coded to the search criteria provided in Appendix 5.

Results/Discussion

Primary Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 23 (7 medically confirmed and 16 medically unconfirmed) post-marketing sources (including spontaneous and solicited), initial, primary dose cases reporting the use with concomitant vaccination were identified. Of these 23 cases, 12 were serious and 11 were nonserious and reported a total of 88 events (25 serious; 63 nonserious).

Cumulatively, 97 (28 medically confirmed and 69 medically unconfirmed) post-marketing sources (including spontaneous and solicited), primary dose cases reporting the use with concomitant vaccination were identified. Of these cases, 43 cases were serious and 54 were nonserious and reported a total of 455 events (125 serious; 330 nonserious).

The most commonly reported co-administered vaccine type (both during the reporting period as well as cumulatively) was the influenza vaccine (interval n=18; cumulatively n=56). An overview of these cases is presented in Table 23 below.

Table 23: Characteristics of Post-marketing, Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Use With Concomitant Vaccination

Case Characteristics		Number of Cases Received During the Interval Reporting Period=23	Number of Cases Received Cumulatively=97
Sex	Male	11	55
	Female	10	39
	NR	2	3
Age (Years)[a]	18 to 35	3	22
Minimum: 30	36 to 50	3	19
Maximum: 95	51 to 64	5	27
Mean: 60.6	≥65	9	24
Median: 58.5	Adult	0	1
	Elderly	1	1
	NR	2	3
Sources	Spontaneous	17	90
	Clinical study (noninterventional; solicited)	3	4
	Clinical study (noninterventional; unsolicited)	2	2
	Interventional clinical trial	1	1
Country/Territory[b]	Brazil	8	13
	United States	6	48
	Belgium	1	2
	Canada	1	2
	Germany	1	2
	Greece	1	1
	Italy	1	2
	Netherlands	1	17
	Poland	1	1
	South Africa	1	2
	Spain	1	3
Event Characteristics		**Number of Events=88**	**Number of Events=455**
Seriousness (Event Level)[c]	Nonserious	63	330
	Serious	25	125
Outcome (Event Level)[c]	Not resolved	24	116
	Resolving	21	85
	Fatal	11	14
	Resolved	5	97
	Resolved with sequelae	0	7
	NR	27	136
Concomitant Vaccine Type[d]	Influenza vaccine	18	56
	Diphtheria vaccine toxoid	2	8
	Tetanus vaccine toxoid	2	14
	Japanese encephalitis vaccine	1	1
	Measles vaccine	1	1

Table 23: Characteristics of Post-marketing, Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Use With Concomitant Vaccination

Case Characteristics		Number of Cases Received During the Interval Reporting Period=23	Number of Cases Received Cumulatively=97
	Pertussis vaccine acellular 4-component	1	1
	Pertussis vaccine acellular 5-component	1	4
	Pneumococcal vaccine	1	4
	Polio vaccine	1	1
	Polio vaccine inact 3V (vero)	1	1
	Typhoid vaccine	1	2
	Varicella zoster vaccine	1	6
	Yellow fever vaccine	1	1

Key: NR=Not Reported

a: The calculation was based on the current reporting period (25 February 2022 to 24 August 2022). Age group was presented for cases where age was not reported.

b: Countries/Territories were presented in decreasing order for the current reporting period (25 February 2022 to 24 August 2022).

c: Seriousness and outcome have been presented for the events. A single case may report more than 1 event.

d: Concomitant vaccines were presented in decreasing order for the current reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 concomitant vaccine.

Of these 23 post-marketing, initial, primary dose cases, the most frequently reported countries/territories of origin (n≥6) were Brazil (n=8), followed by the US (n=6). These cases concerned 11 males, 10 females, and 2 did not report sex. The age range was from 30 to 95 years.

The frequency distribution of the MedDRA PTs reported in post-marketing, primary dose cases is presented in Table 24 below. A single case may contain more than 1 event.

Table 24: Frequency of MedDRA PTs in Post-marketing, Primary Dose Cases Reporting Use With Concomitant Vaccination With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Pyrexia	1	7	1	20
Fatigue	0	4	1	16
Suspected COVID-19	0	4	1	5
Vaccination failure	4	0	10	0
Arthralgia	0	3	1	9
Diarrhoea	0	3	1	6
Myalgia	0	3	0	8
Pain	0	3	2	8
Pulmonary embolism	3	0	4	0

Table 24: Frequency of MedDRA PTs in Post-marketing, Primary Dose Cases Reporting Use With Concomitant Vaccination With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: The MedDRA PTs with a frequency ≥3 have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event.

The most frequently reported events (n≥4) included pyrexia (n=8), and fatigue, suspected COVID-19, and vaccination failure (n=4 each). The mean and median time to onset (TTO) were 49.8 days and 1 day respectively. Where reported (n=61), the outcomes were not resolved (n=24), resolving (n=21), fatal (n=11), and resolved (n=5).

Of the 23 post-marketing, initial, primary dose cases reported during the reporting period of 25 February 2022 to 24 August 2022, in 6 the dates of concomitant vaccine administration were specified. Dates of vaccination were not specified for the remaining 17 cases. An overview of these cases is included in Table 25.

Table 25: Overview of MedDRA PTs in Post-marketing, Primary Dose Cases Reporting the Use of Ad26.COV2.S With Concomitant Vaccinations During the Reporting Period (Cases=23)

MedDRA PTs	Number of Events[a]
Cases reporting specified dates of concomitant vaccine administration (n=6)	
Pyrexia	4
Diarrhoea	3
Pulmonary embolism	3
Cases reporting unspecified dates of concomitant vaccine administration (n=17)	
Pyrexia	4
Suspected COVID-19	4
Vaccination failure	4
Fatigue	3

Key: COVID-19=Coronavirus Disease-2019; MedDRA=Medical Dictionary for Regulatory Activities; n=Number of Cases; PT=Preferred Term
a: A single case may report more than 1 MedDRA PT. MedDRA PTs with frequency ≥3 have been presented.

Fatal Post-marketing Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 4 post-marketing, primary dose fatal cases with 11 fatal events were retrieved. The fatal event was pulmonary embolism, which occurred in 3 elderly patients (aged 71, 78 and 95 years) who received influenza vaccine on the same day as Ad26.COV2.S. The remaining case involved an adult patient (aged 51 years), with underlying alcohol addiction, nicotine abuse, chronic obstructive pulmonary disease (COPD), and alcoholic steatohepatitis, who experienced general physical health deterioration, hypoglycaemia, hypoxia, multiple organ dysfunction syndrome, pyrexia, respiratory failure, resuscitation, and tachycardia. The patient had received the diphtheria, pertussis, polio and tetanus vaccines, 1 month

and 17 days after Ad26.COV2.S administration. No information on concomitant medication and clinical course/diagnosis of the events was provided.

Booster Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 36 (7 medically confirmed and 29 medically unconfirmed) post-marketing sources (including spontaneous and solicited), initial cases reported as booster were identified. There were 13 serious and 23 nonserious cases and reported a total of 226 events (38 serious; 188 nonserious). Of these cases, 28 were heterologous and 8 were homologous.

Cumulatively, 60 (9 medically confirmed and 51 medically unconfirmed) post-marketing sources (including spontaneous and solicited) cases reported as booster were identified. Of these cases, 26 were serious and 34 were nonserious and reported a total of 347 events (72 serious; 275 nonserious). Of these cases, 38 were heterologous and 22 were homologous.

The most commonly reported coadministered vaccine type (both during the reporting period as well as cumulatively) was the influenza vaccine (interval n=34; cumulatively n=56).

A cumulative booster dose CIOMS II LL is presented in Appendix 6.2.

An overview of these cases is presented in Table 26 below.

Table 26: Characteristics of Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Use With Concomitant Vaccination

Case Characteristics		Number of Cases Received During the Interval Reporting Period=36	Number of Cases Received Cumulatively=60
Sex	Female	21	34
	Male	14	25
	NR	1	1
Age (Years)[a]	<18	1	1
Minimum: 13	18 to 35	1	3
Maximum: 81	36 to 50	0	7
Mean: 62.2	51 to 64	14	22
Median: 64	≥65	12	16
	Neonate	2	2
	Adult	1	1
	Elderly	1	1
	NR	4	7
Country/Territory[b]	Brazil	27	29
	United States	5	24
	Germany	3	3
	Portugal	1	1
Sources	Spontaneous	28	50
	Clinical study (noninterventional; solicited)	5	7

Table 26: Characteristics of Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Use With Concomitant Vaccination

Case Characteristics		Number of Cases Received During the Interval Reporting Period=36	Number of Cases Received Cumulatively=60
	Clinical study (noninterventional; unsolicited)	3	3
Classification	Heterologous	28	38
	Homologous	8	22
Event Characteristics		**Number of Events=226**	**Number of Events=347**
Seriousness (Event Level)[c]	Nonserious	188	275
	Serious	38	72
Outcome (Event Level)[c]	Resolving	59	86
	Not resolved	49	62
	Resolved	33	80
	Fatal	1	2
	NR	84	117
Concomitant Vaccine Type[d]	Influenza vaccine	34	56
	Diphtheria vaccine toxoid	2	3
	Pertussis vaccine acellular	2	3
	Tetanus vaccine toxoid	2	3
	Meningococcal vaccine	1	1

Key: NR=Not Reported

a: The calculation was based on the current reporting period (25 February 2022 to 24 August 2022). Age group was presented for cases where age was not reported.

b: Countries/Territories were presented in decreasing order for the current reporting period (25 February 2022 to 24 August 2022).

c: Seriousness and outcome have been presented for the events. A single case may report more than 1 event.

d: Concomitant vaccines were presented in decreasing order for the current reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 concomitant vaccine.

Of these 36 post-marketing, initial cases reported as booster, the most frequently reported countries/territories of origin (n≥5) were Brazil (n=27), followed by the US (n=5). These cases concerned 21 females, 14 males, and 1 did not report sex. The age range was from 13 to 81 years.

The frequency distribution of the MedDRA PTs reported in post-marketing cases reported as booster is presented in Table 27 below. A single case may contain more than 1 event.

Table 27: Frequency of MedDRA PTs in Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Use With Concomitant Vaccination

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Off label use	0	24	0	26
Inappropriate schedule of product administration	0	13	0	15
Fatigue	0	12	1	16
Pyrexia	1	11	2	14
Headache	0	10	2	13
Dizziness	0	8	1	9
Injection site pain	0	7	0	11
Malaise	0	7	0	8
Chills	0	6	1	9
COVID-19	1	4	2	7
Myalgia	0	5	0	6
Arthralgia	0	4	0	7
Asthenia	0	4	0	5
Feeling abnormal	0	4	0	6

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

a: The MedDRA PTs with a frequency ≥4 have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event.

The most frequently reported events (n≥10) included off label use (n=24), inappropriate schedule of product administration (n=13), fatigue and pyrexia (n=12 each), and headache (n=10). The mean and median TTO were 32.8 days and same day, respectively. Where reported (n=142), the outcomes were resolving (n=59), not resolved (n=49), resolved (n=33), and fatal (n=1).

Of the 36 post-marketing, initial cases reported as booster during the reporting period of 25 February 2022 to 24 August 2022, in 9, the dates of concomitant vaccine administration were specified. Dates of vaccination were not specified for the 27 cases. An overview of these cases is included in Table 28.

Table 28: Overview of MedDRA PTs in Post-marketing Cases Reported as Booster Reporting the Use of Ad26.COV2.S With Concomitant Vaccinations During the Reporting Period (Cases=36)

MedDRA PTs	Number of Events[a]
Cases reporting specified dates of concomitant vaccine administration (n=9)	
Off label use	9
Inappropriate schedule of product administration	7
Pyrexia	4
Cases reporting unspecified dates of concomitant vaccine administration (n=27)	
Off label use	15
Fatigue	10
Headache	8
Pyrexia	8
Dizziness	7
Malaise	7

Table 28: Overview of MedDRA PTs in Post-marketing Cases Reported as Booster Reporting the Use of Ad26.COV2.S With Concomitant Vaccinations During the Reporting Period (Cases=36)

MedDRA PTs	Number of Events[a]
Inappropriate schedule of product administration	6
COVID-19	5
Chills	4
Injection site pain	4

Key: COVID-19=Coronavirus Disease-2019; MedDRA=Medical Dictionary for Regulatory Activities; n=Number of Cases; PT=Preferred Term

a: A single case may report more than 1 MedDRA PT. MedDRA PTs with frequency ≥4 have been presented.

Fatal Post-marketing Booster Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 1 initial, fatal case reported as booster with 1 fatal event was retrieved. The fatal event was acute respiratory distress syndrome which occurred in the context of pulmonary embolism and COVID-19 infection.

Literature ICSR

The single ICSR literature case received during the reporting period of 25 February 2022 to 24 August 2022 was reviewed, and no new information concerning concomitant vaccination was identified.

Conclusion

Most of the events reported in patients receiving Ad26.COV2.S with concomitant vaccines were reactogenic and/or listed for Ad26.COV2.S. No trend in events, including those with fatal outcome 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.

15.4. Vaccination Anxiety-related Reactions

Introduction

Vaccination anxiety-related reactions such as syncope are included within the PBRER in line with the GVP Module on Vaccines (Product- or Population-Specific Considerations I: Vaccines for prophylaxis against infectious diseases). The CIOMS/WHO Working Group on Vaccine Pharmacovigilance notes that the types of reactions caused by vaccination anxiety include, but are not limited to, vasovagal mediated reactions, hyperventilation mediated reactions, and stress-related psychiatric disorders.

Methods

The Company global safety database was searched for medically confirmed and medically unconfirmed cases received during this reporting period and cumulatively which coded to the search criteria provided in Appendix 5.

Results/Discussion

Primary Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 1,029 (489 medically confirmed and 540 medically unconfirmed) initial, primary dose cases reporting vaccination anxiety-related reactions were identified. Of these 1,029 cases, 620 were serious and 409 were nonserious and reported a total of 1,181 EOI (647 serious; 534 nonserious). Of the 1,029 primary dose cases, 308 met the criteria as vaccination anxiety-related reactions. Of the 308 cases, 253 were medically confirmed and 251 cases were serious.

Of these 308 primary dose cases meeting criteria for vaccination anxiety-related reactions during the interval reporting period, all were from post-marketing sources (including spontaneous and solicited cases). No cases were from Janssen Sponsored Clinical Studies or Janssen Supported Clinical Studies.

Cumulatively, 5,064 (1,644 medically confirmed and 3,420 medically unconfirmed) primary dose cases reporting vaccination anxiety-related reactions were identified. Of these cases, 2,656 were serious and 2,408 were nonserious and reported a total of 5,735 EOI (2,623 serious; 3,112 nonserious). Of the 5,064 cumulative cases, 1,210 met the criteria as vaccination anxiety-related reactions. Of the 1,210 cases, 791 were medically confirmed and 902 were serious.

Of the 1,210 cumulative primary dose cases meeting criteria, all were from post-marketing sources (including spontaneous and solicited cases). No cases were from Janssen Sponsored Clinical Studies or Janssen Supported Clinical Studies.

Janssen Sponsored and Janssen Supported Clinical Studies (Primary Dose Cases)

There were no initial, primary dose cases meeting criteria as vaccination anxiety-related reactions from the search of the Company global safety database during the reporting period of 25 February 2022 to 24 August 2022 for either the Janssen Sponsored or Janssen Supported Clinical Studies.

Post-marketing Sources (Including Spontaneous and Solicited) Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 308 post-marketing sources (including spontaneous and solicited), initial, primary dose cases met criteria for vaccination anxiety-related reactions. Of these 308 cases, 251 were serious and 57 nonserious and reported a total of 385 EOI (278 serious; 107 nonserious).

Cumulatively, 1,210 (791 medically confirmed and 419 medically unconfirmed) post-marketing, primary dose cases met criteria for vaccination anxiety-related reactions. Of these cases, 902 were serious and 308 were nonserious and reported a total of 1,488 EOI (1,019 serious; 469 nonserious).

An overview of these cases is presented in Table 29 below.

Table 29: Characteristics of Post-marketing Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Vaccination Anxiety-related Reactions

Case Characteristics		Number of Cases Received During the Interval Reporting Period=308	Number of Cases Received Cumulatively=1,210
Sex	Male	135	699
	Female	100	408
	NR	73	103
Age (Years)[a]	<18	0	4
Minimum: 18	18 to 35	202	723
Maximum: 73	36 to 50	68	240
Mean: 32.3	51 to 64	22	135
Median: 30.0	≥65	6	27
	Adult	0	26
	NR	10	55
Sources	Spontaneous	302	1,196
	Clinical study (noninterventional; solicited)	6	14
Country/Territory[b]	Romania	102	127
	Poland	89	102
	South Africa	26	44
	Germany	23	100
	Philippines	22	90
	Ireland	11	61
Event Characteristics		**Number of Events=385**	**Number of Events=1,488**
Seriousness (Event Level)[c]	Serious	278	1,019
	Nonserious	107	469
Outcome (Event Level)[c]	Resolved	161	885
	Resolving	27	165
	Not resolved	9	65
	Resolved with sequelae	3	9
	Fatal	0	5
	NR	185	359

Key: NR=Not Reported

a: The calculation was based on the current reporting period (25 February 2022 to 24 August 2022). Age group was presented for cases where age was not reported.

b: Countries/Territories with frequency >10 were presented in decreasing order for the current reporting period (25 February 2022 to 24 August 2022).

c: Seriousness and outcome have been presented for the events of interest. A single case may report more than 1 event of interest.

Of these 308 post-marketing, initial, primary dose cases, the most frequently reported countries/territories of origin (n≥89) were Romania (n=102), followed by Poland (n=89). These cases concerned 135 males, 100 females, and 73 did not report sex. The age range was from 18 to 73 years.

Table 30 describes the sex/age reported in the 308 cases identified as vaccination anxiety-related reactions.

Table 30: Demographics for Ad26.COV2.S Vaccination Anxiety-related Reactions Cases Reported During the Reporting Interval (Cases=308)

Sex/Age	Number of Cases
Male	**135**
18 to 29 years	68
30 to 49 years	55
50 to 69 years	8
70+ years	0
NR	4
Female	**100**
18 to 29 years	39
30 to 49 years	38
50 to 69 years	17
70+ years	2
NR	4
Age and/or Sex Not Reported	**73**
18 to 29 years	32
30 to 49 years	35
50 to 69 years	4
NR	2

Key: NR=Not Reported

The 308 cases of vaccination anxiety-related reactions reported 385 EOI. The vaccination anxiety-related EOI identified in these cases are described in Table 31 below:

Table 31: MedDRA PTs of Interest and Their Outcomes Reported in Cases Identified as Vaccination Anxiety-related Reactions (Events =385)

MedDRA Preferred Terms	Event Outcome					
	Not Resolved	Resolved	Resolved With Sequelae	Resolving	Not Reported	Total
Syncope	3	73	1	13	108	198
Loss of consciousness	0	35	0	4	22	61
Hyperhidrosis	2	25	0	2	14	43
Pallor	0	10	0	2	17	29
Anxiety	2	5	2	2	8	19
Presyncope	1	7	0	1	8	17
Hypotonia	1	1	0	0	4	6
Nervousness	0	2	0	1	0	3
Fear	0	2	0	0	0	2
Stress	0	0	0	1	1	2
Unresponsive to stimuli	0	0	0	0	2	2
Depressed level of consciousness	0	0	0	1	0	1
Fear of injection	0	0	0	0	1	1
Skin discolouration	0	1	0	0	0	1
Total	**9**	**161**	**3**	**27**	**185**	**385**

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

Of the 251 serious cases, the criteria included life-threatening (n=1), hospitalisation (n=6), disability (n=2), and other medically important events (n=242).

The frequency distribution of the MedDRA PTs of interest reported in post-marketing, primary dose cases is presented in Table 32 below. A single case may contain more than 1 EOI.

Table 32: Frequency of MedDRA PTs of Interest in Post-marketing, Primary Dose Cases Reporting Vaccination Anxiety-related Reactions With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Syncope	198	0	614	0
Loss of consciousness	61	0	214	0
Hyperhidrosis	8	35	60	144
Pallor	2	27	40	57
Anxiety	3	16	9	54
Presyncope	2	15	51	160
Hypotonia	0	6	3	11
Nervousness	1	2	1	14
Fear	0	2	0	8
Stress	0	2	0	6
Unresponsive to stimuli	2	0	10	0
Depressed level of consciousness	1	0	5	0
Fear of injection	0	1	0	1
Skin discolouration	0	1	0	4

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

a: The MedDRA PTs of interest have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event of interest. The PTs that were reported cumulatively but not reported in the interval include hypokinesis (n=9), shock (n=6), altered state of consciousness (n=2), seizure-like phenomena (n=2), tension (n=2), and immunisation stress-related response (n=1).

The EOI identified during the reporting interval included syncope (n=198), loss of consciousness (n=61), hyperhidrosis (n=43), pallor (n=29), anxiety (n=19), presyncope (n=17), hypotonia (n=6), nervousness (n=3), fear, stress, and unresponsive to stimuli (n=2 each), and depressed level of consciousness, fear of injection, and skin discolouration (n=1 each). The mean and median TTO was 0 days. Where reported (n=200), the outcomes were resolved (n=161), resolving (n=27), and not resolved (n=9), and resolved with sequelae (n=3).

Fatal Post-marketing Primary Dose Cases

There were no fatal, initial post-marketing primary dose cases meeting the criteria for vaccination anxiety-related reaction during the interval reporting period of 25 February 2022 to 24 August 2022.

Booster Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 100 (20 medically confirmed and 80 medically unconfirmed) initial cases reported as booster were identified. There were 47 serious and 53 nonserious cases and reported a total of 114 EOI (37 serious;

77 nonserious). Of the 100 cases reported as booster, 5 met the criteria as vaccination anxiety-related reactions. Of the 5 cases, 2 were medically confirmed and 3 were serious. All 5 cases were homologous.

Of these 5 cases reported as booster during the interval, all were from post-marketing sources (including spontaneous and solicited cases). No cases were from Janssen Sponsored Clinical Studies or Janssen Supported Clinical Studies.

Cumulatively, 158 (32 medically confirmed and 126 medically unconfirmed) cases reported as booster were identified. Of these cases, 75 were serious and 83 were nonserious and reported a total of 183 EOI (56 serious; 127 nonserious). Of the 158 cumulative cases, 9 met the criteria as vaccination anxiety-related reactions. Of the 9 cases, 3 were medically confirmed and 4 were serious. Of these cases, 7 were homologous and 2 were heterologous.

Of the 9 cumulative cases reported as booster, all were from post-marketing sources (including spontaneous and solicited cases). No cases were from Janssen Sponsored Clinical Studies or Janssen Supported Clinical Studies.

A cumulative booster dose CIOMS II LL is presented in Appendix 6.3.

Janssen Sponsored and Janssen Supported Clinical Studies (Booster Dose Cases)

There were no initial cases reported as booster which met the criteria for vaccination anxiety-related reactions during the interval reporting period of 25 February 2022 to 24 August 2022 for either the Janssen Sponsored or Janssen Supported Clinical Studies.

Post-marketing Sources (Including Spontaneous and Solicited) Booster Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 5 post-marketing sources (including spontaneous and solicited), initial cases reported as booster were retrieved. These 5 post-marketing booster dose cases reported 6 EOI (4 serious; 2 nonserious).

Cumulatively, 9 (3 medically confirmed and 6 medically unconfirmed) post-marketing cases reported as booster were identified. Of these cases, 4 were serious and 5 were nonserious and reported a total of 11 EOI (5 serious; 6 nonserious).

An overview of these cases is presented in Table 33 below.

Table 33: Characteristics of Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Vaccination Anxiety-related Reactions

Case Characteristics		Number of Cases Received During the Interval Reporting Period=5	Number of Cases Received Cumulatively=9
Sex	Female	4	8
	Male	1	1

Table 33: Characteristics of Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Vaccination Anxiety-related Reactions

Case Characteristics		Number of Cases Received During the Interval Reporting Period=5	Number of Cases Received Cumulatively=9
Age (Years)[a]	18 to 35	0	1
Minimum: 37	36 to 50	3	4
Maximum: 47	≥65	0	1
Mean: 41.3	Adult	1	1
Median: 40.0	NR	1	2
Country/Territory[b]	United States	2	5
	South Africa	2	2
	Poland	1	1
Sources	Spontaneous	5	9
Classification	Homologous	5	7
	Heterologous	0	2
Event Characteristics		**Number of Events=6**	**Number of Events=11**
Seriousness (Event Level)[c]	Serious	4	5
	Nonserious	2	6
Outcome (Event Level)[c]	Resolved	4	5
	Resolving	1	2
	Not resolved	0	1
	NR	1	3

Key: NR=Not Reported
a: The calculation was based on the current reporting period (25 February 2022 to 24 August 2022). Age group was presented for cases where age was not reported.
b: Countries/Territories were presented in decreasing order for the current reporting period (25 February 2022 to 24 August 2022).
c: Seriousness and outcome have been presented for the events of interest. A single case may report more than 1 event of interest.

Of these 5 post-marketing, initial cases reported as booster, the most frequently reported countries/territories of origin were South Africa and the US (n=2 each), followed by Poland (n=1). These cases concerned 4 females and 1 male. The age range was from 37 to 47 years.

Table 34 describes the sex/age reported in the 5 cases identified as vaccination anxiety-related reactions.

Table 34: Demographics for Ad26.COV2.S Vaccination Anxiety-related Reactions Cases Reported as Booster During the Reporting Interval (Cases=5)

Sex/Age	Number of Cases
Male	**1**
NR	1
Female	**4**
30 to 49 years	3
NR	1

Key: NR=Not Reported

The 5 cases of vaccination anxiety-related reactions reported as booster reported 6 EOI. The vaccination anxiety-related EOI identified in these cases are described in Table 35 below:

Table 35: MedDRA PTs of Interest and Their Outcomes in Post-marketing Cases Reported as Booster With Use of Ad26.COV2.S and Reporting Vaccination Anxiety-related Reactions (Events =6)

MedDRA PTs	Event Outcome			
	Resolved	Resolving	Not Reported	Total
Hyperhidrosis	1	1	0	2
Loss of consciousness	1	0	1	2
Syncope	2	0	0	2
Total	**4**	**1**	**1**	**6**

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

The case serious criteria included was other medically important events (n=3).

The frequency distribution of the MedDRA PTs of interest reported in post-marketing cases reported as booster is presented in Table 36 below. A single case may contain more than 1 EOI.

Table 36: Frequency of MedDRA PTs of Interest in Post-marketing Cases Reported as Booster With Use of Ad26.COV2.S and Reporting Vaccination Anxiety-related Reactions

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Hyperhidrosis	0	2	0	2
Loss of consciousness	2	0	3	0
Syncope	2	0	2	0

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

a The MedDRA PTs of interest have been presented for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event of interest.

The EOI included hyperhidrosis, loss of consciousness, and syncope (n=2 each). The mean and median TTO was 0 days. Where reported (n=5), the outcomes were resolved (n=4) and resolving (n=1).

Fatal Post-marketing Booster Dose Cases

There were no fatal, initial cases reported as booster which were retrieved from the search of the Company global safety database during the interval reporting period of 25 February 2022 to 24 August 2022.

Literature ICSR

ICSR literature cases received during the reporting period of 25 February 2022 to 24 August 2022 were reviewed, and no information was identified that would change the characterisation of risk.

Discussion

For the reporting interval of 25 February 2022 to 24 August 2022, 308 cases meeting the criteria for vaccination anxiety-related reactions were reported and this is comparable to the number of cases identified for the PBRER reporting interval of 25 August 2021 to 24 February 2022 (n=398). However, 81% (n=250) of the cases for the current interval were reported from the EVHUMAN database and contained limited information on exact TTO, medical history, concomitant medications, or clinical course of the event. These cases were conservatively assessed as vaccination anxiety-related reactions as they occurred on the same day as vaccination with no other events reported and this included 1 case which was reported as life-threatening. The majority of these cases (62%) are from Romania (n=102) and Poland (n=89). As was seen in previous reporting intervals, the majority of the cases identified as vaccination anxiety-related reactions occurred in male patients between the ages of 18 and 49.

Conclusion

A review of the cases of anxiety-related reactions identified in the current interval confirmed these are consistent with the known safety data for these events including rapid TTO and typically transient in nature.

Anxiety-related reactions were previously assessed as a signal for Ad26.COV2.S and it has been concluded that these anxiety-reactions to immunisation are a complication of the immunisation process. The CIOMS/WHO Working Group on Vaccine Pharmacovigilance notes that the types of reactions caused by vaccination anxiety include but are not limited to vasovagal mediated reactions, hyperventilation mediated reactions, and stress-related psychiatric disorders.

Based on a review of all available data, no new safety issues were identified for vaccination anxiety-related reactions. Vaccination anxiety-related reactions such as syncope will be discussed in future PBRERs in line with the GVP Module on Vaccines (Product- or Population-Specific Considerations I: Vaccines for prophylaxis against infectious diseases).

15.5. Vaccine Failure, Lack of Efficacy/Effectiveness

Introduction

Vaccine failure, or lack of efficacy/effectiveness (LOE) is included within the PBRER in line with the GVP Module on Vaccines (Product or Population-Specific Considerations I: Vaccines for prophylaxis against infectious diseases).

Vaccine-associated enhanced disease (VAED), including Vaccine-associated Enhanced Respiratory Disease (VAERD) is considered an Important Potential Risk in the cRMP for

Ad26.COV2.S, based on past experiences in the development of vaccines against Respiratory syncytial virus (RSV), Dengue virus, SARS-CoV-1, and Middle East Respiratory Syndrome Related Coronavirus (MERS-CoV).

Confirmed vaccination failure is defined as the occurrence of the specific vaccine preventable-disease in a person who is appropriately and fully vaccinated and taking into account the incubation period and the normal delay for the protection to be acquired as a result of immunisation. This definition requires clinical and laboratory confirmation that the disease is specifically targeted by the vaccine (eg COVID-19 PCR positive test, antigen test).]

Methods

The Company global safety database was searched for medically confirmed and medically unconfirmed cases received during this reporting period and cumulatively, which coded to the search criteria provided in Appendix 5.

Results/Discussion

Primary Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 4,950 post-marketing (4,672 medically confirmed and 278 medically unconfirmed) primary dose cases reporting events of vaccine failure or LOE were identified. Of these 4,950 cases, 4,711 were serious and 239 were nonserious and reported a total of 9,522 EOI (9,138 serious, 384 nonserious).

Cumulatively, 13,868 post-marketing (11,469 medically confirmed and 2,399 medically unconfirmed) primary dose cases reporting events of vaccine failure or LOE were identified. Of these 13,868 cases, 12,137 were serious and 1,731 were nonserious and reported a total of 24,579 EOI (21,864 serious, 2,715 nonserious).

Janssen Sponsored and Janssen Supported Clinical Studies (Primary Dose Cases)

Information on Janssen Sponsored and Janssen Supported Clinical Studies can be found in Section 13, Lack of Efficacy in Controlled Clinical Trials and Section 17, Benefit Evaluation of the PBRER.

Post-marketing Sources (Including Spontaneous and Solicited) Primary Dose Cases

An overview of the 4,950 (interval) and 13,868 (cumulative) post-marketing primary dose cases is presented in Table 37 below.

Table 37: Characteristics of Post-marketing, Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Vaccine Failure, Lack of Efficacy/Effectiveness

Case Characteristics		Number of Cases Received During the Interval Reporting Period=4,950	Number of Cases Received Cumulatively=13,868
Sex	Male	2,925	7,563
	Female	1,903	5,046
	NR	122	1,259
Age (Years)[a]	<18	10[b]	29[b]
Minimum:0.082	18 to 35	2,095	5,701
Maximum:101	36 to 50	1,583	3,846
Mean: 39.8	51 to 64	867	2,352
Median: 38	≥65	271	964
	Neonate	5	9
	Infant	2	2
	Adult	15	48
	Elderly	2	7
	NR	100	909
Sources	Spontaneous	4,888	13,726
	Clinical study (noninterventional, solicited)	59	139
	Clinical study (noninterventional, unsolicited)	3	3
Country/Territory[c]	Austria	4,345	8,777
	United States	260	2,039
	Iceland	69	854
	South Africa	39	63
	Germany	37	370
	Philippines	32	274
	Lithuania	25	74
	Canada	23	29
	Greece	17	48
	Portugal	17	559
	Belgium	13	65
	Brazil	12	102
	France	8	169
	Italy	8	56
	Poland	7	27
	Spain	7	64
	Netherlands	6	64
	Estonia	5	59
Event Characteristics		**Number of Events=9,522**	**Number of Events=24,579**
Seriousness Criteria (Event Level)[d]	Other medically important condition	8,901	20,221
	Hospitalisation	127	993
	Death	58	341
	Life-threatening	31	258

Table 37: Characteristics of Post-marketing, Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Vaccine Failure, Lack of Efficacy/Effectiveness

Case Characteristics		Number of Cases Received During the Interval Reporting Period=4,950	Number of Cases Received Cumulatively=13,868
	Disability	21	51
	Nonserious	384	2,715
Seriousness (Event Level)[d]	Serious	9,138	21,864
	Nonserious	384	2,715
Outcome (Event Level)[d]	Resolved	152	1,006
	Not resolved	100	750
	Resolving	68	496
	Fatal	58	341
	Resolved with sequelae	3	9
	NR	9,141	21,977

Key: NR=Not Reported

a: The calculation was based on the current reporting period (25 February 2022 to 24 August 2022). Age group was presented for cases where age was not reported.

b: Includes neonates/infants ages 4 to 18 weeks who experienced foetal exposure during pregnancy; vaccine was not administered.

c: Countries/Territories are listed in descending frequency (≥5) for the current reporting period (25 February 2022 to 24 August 2022).

d: Seriousness criteria, 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 MedDRA PTs of interest reported in post-marketing, primary dose cases is presented in Table 38 below. A single case may contain more than 1 EOI.

Table 38: Frequency of MedDRA PTs of Interest in Post-marketing, Primary Dose Cases Reporting Vaccine Failure, Lack of Efficacy/Effectiveness With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Received During the Interval Reporting Period[a] (Events=9,522)		Number of Events Received Cumulatively (Events=24,579)	
	Serious	Nonserious	Serious	Nonserious
COVID-19	4,426	159	9,542	871
Vaccination failure	4,522	0	10,807	0
SARS-CoV-2 test positive	60	103	238	1,072
Suspected COVID-19	24	98	130	629
Thrombosis with thrombocytopenia syndrome	28	0	73	0
COVID-19 pneumonia	27	0	216	0
Drug ineffective	17	0	179	3
Asymptomatic COVID-19	3	7	17	37
Breakthrough COVID-19	3	5	3	6
SARS-CoV-2 test negative	8	0	73	24
Post-acute COVID-19 syndrome	3	2	8	8

Key: COVID-19=Coronavirus disease-2019; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term; SARS-CoV-2=Severe Acute Respiratory Syndrome Coronavirus-2

Table 38: Frequency of MedDRA PTs of Interest in Post-marketing, Primary Dose Cases Reporting Vaccine Failure, Lack of Efficacy/Effectiveness With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Received During the Interval Reporting Period[a] (Events=9,522)		Number of Events Received Cumulatively (Events=24,579)	
	Serious	Nonserious	Serious	Nonserious

a: The MedDRA PTs of interest with a frequency ≥5 have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event of interest.

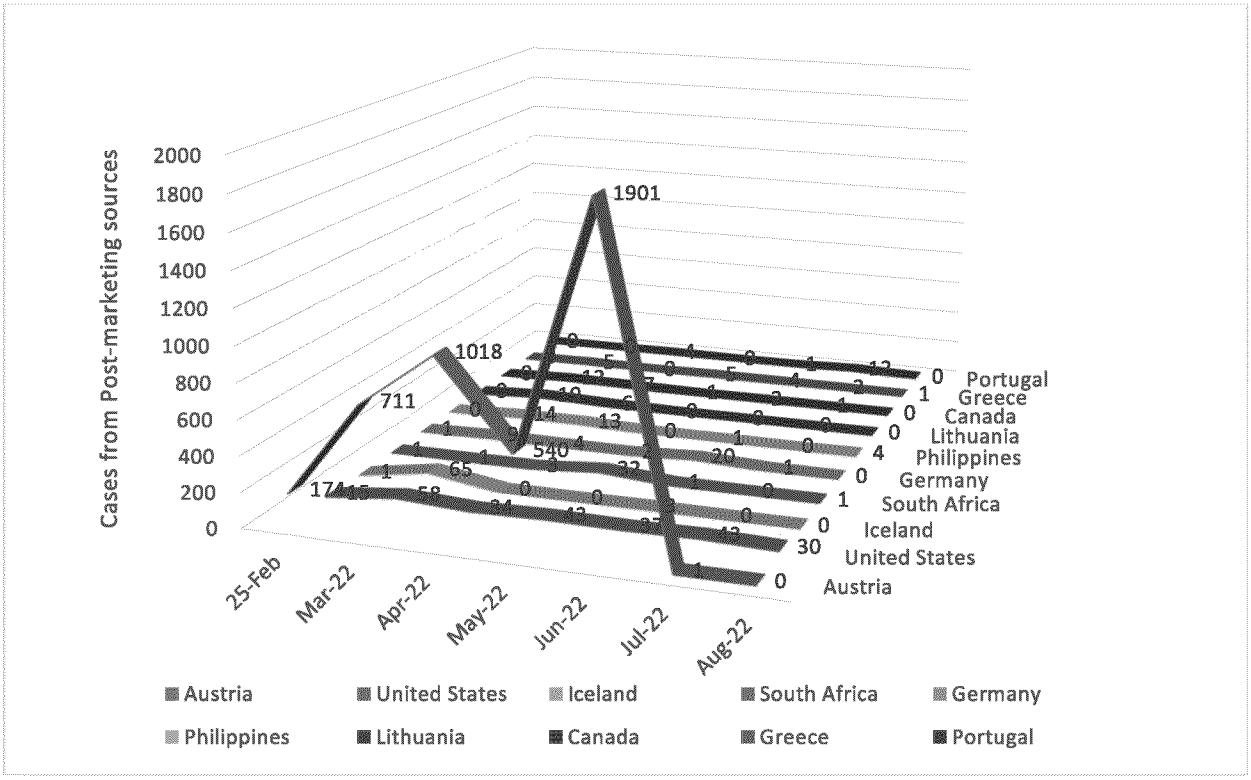
These 4,950 cases reported 9,138 serious EOI. Of these 4,950 cases, the most frequently reported country/territory of origin was Austria (n=4,345) followed by the US (n=260) and Iceland (n=69). Of the 4,950 cases, 2,925 cases concerned males, 1,903 females, and 122 had no sex reported. The age range was 0.082 to 101 years.

The EOI (≥122) included COVID-19 (n=4,585), vaccination failure (n=4,522), SARS-CoV-2 test positive (n=163), and suspected COVID-19 (n=122).

The outcomes for the total 9,522 EOI received during the reporting period, where reported (n=381), the outcomes were resolved (n=152), not resolved (n=100), resolving (n=68), fatal (n=58), and resolved with sequelae (n=3).

Figure 1 below depicts the post-marketing (including spontaneous and solicited) primary dose case count from the top 10 countries/territories by month.

Figure 1: Post-marketing Primary Dose Cases Reporting Vaccine Failure, Lack of Efficacy/Effectiveness With the Use of Ad26.COV2.S From the Top 10 Countries/Territories by Month



The TTO reported in these 4,950 cases is presented in Table 39.

Table 39: Time to Onset in Primary Dose Cases Involving the Use of Ad26.CoV2.S and Reporting Vaccine Failure, Lack of Efficacy/Effectiveness (Cases=4,950)

TTO	Number of Cases
≤14 days	43
>14 days but ≤28 days	26
>28 days	4,668
NA[a]	9
NR	204
Total[b]	**4,950**

Key: NA=Not Applicable; NR=Not Reported; PBRER=Periodic Benefit Risk Evaluation Report; TTO=Time to Onset

a: These cases reported foetal exposure during pregnancy; vaccine was not administered to neonate/infant.

b: TTO categories have been presented at the case level in the current PBRER, as compared to the event level presented in the previous PBRER.

Laboratory findings reported are provided in Table 40 below.

Table 40: Laboratory Findings in Primary Dose Cases Involving the Use of Ad26.CoV2.S and Reporting Vaccine Failure, Lack of Efficacy/Effectiveness (Cases=4,950)

Laboratory Findings	Number of Cases
COVID-19 test positive	4,668
COVID-19 test negative	20
Antibody test negative	7
Antibody test positive	1
NR	254

Key: COVID-19=Coronavirus Disease-2019; NR=Not Reported

Of the 4,950 post-marketing primary dose cases, 4 cases reported information on variant sequencing; Alpha (1), B.1.617.2 lineage (1), Delta (1), and the remaining case reported coinfection with both Omicron and Delta variant. Three of these cases were not fatal, life-threatening, required hospitalisation or were disabling. However, the remaining case, reporting PCR-verified Alpha variant was fatal. This case concerned a 7-decade-old lung transplant patient (sex not reported) who worked in a correctional facility with 250+ reported cases of COVID-19. Concomitant medications included mycophenolate mofetil, prednisone, and tacrolimus. The patient experienced fever, cough, and dyspnoea, 62 days after receiving Ad26.COV.2.S and was treated with remdesivir and dexamethasone. The patient developed severe hypoxemia, sustained cardiac arrest, renal failure requiring dialysis colitis, pneumonia related to *Pseudomonas*, and multiple secondary infections and subsequently died. VAERD could not be ruled out given the patient's severe hypoxemia. However, the patient's medical history of lung transplantation likely contributed to the severity of COVID-19 illness.

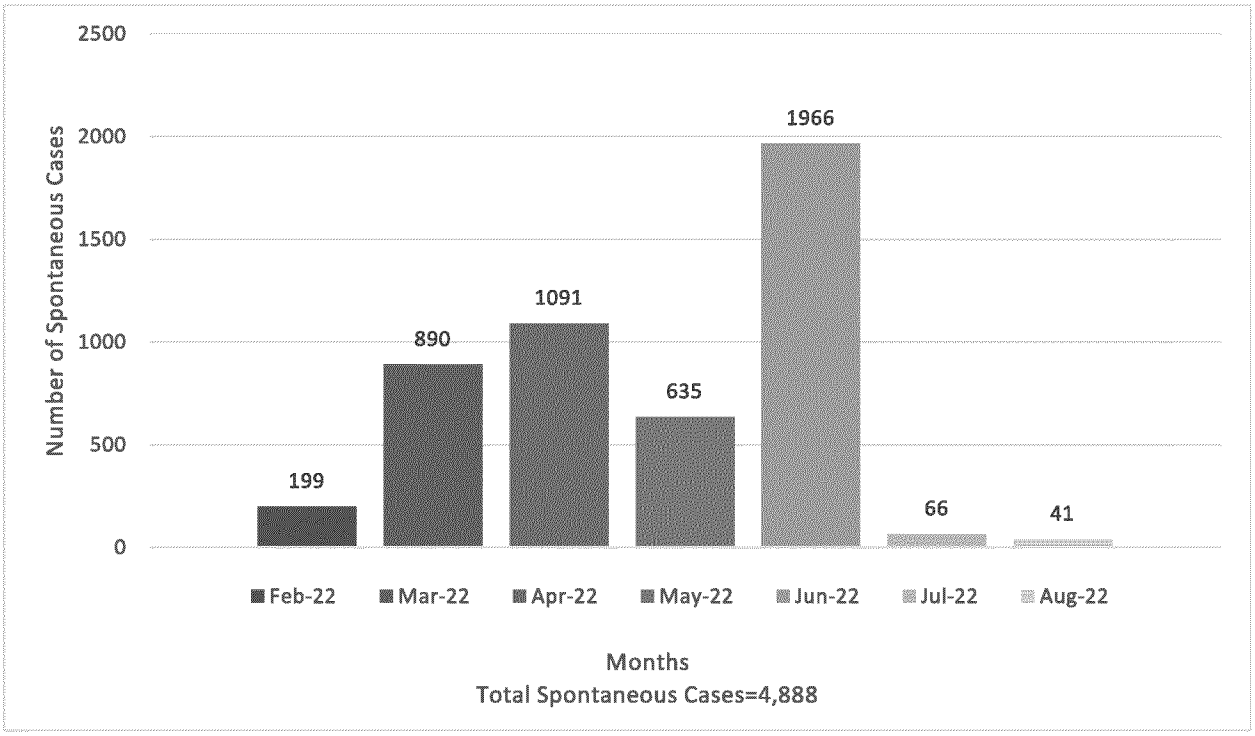
The Company case definition of vaccination failure is as follows: medically confirmed, TTO >14 days, and positive COVID-19 testing; 4,530 of the 4,950 post-marketing primary dose cases met this case definition. Additionally, 38 of the 4,950 cases also reported suspected

vaccination failure. In these 38 cases, TTO was greater than 14 days and were medically confirmed; however, no laboratory test results were specified.

Note that in the previous reporting period (25 August 2021 to 24 February 2022), the number of cases meeting criteria of vaccination failure/LOE was erroneously reported as 112 cases. The correct total was 3,110 cases. As all cases meeting search criteria received during the reporting interval were considered in the conclusions, there was no change to the benefit-risk analysis as a result of this error.

Figure 2 depicts the monthly spontaneous case count (primary dose) from February 2022 to August 2022.

Figure 2: Case Count of Post-Marketing marketing Primary Dose Spontaneous Cases by Month Involving the Use of Ad26.COV2.S and Reporting Vaccine Failure, Lack of Efficacy/Effectiveness



The events are further sorted by seriousness and their respective outcomes in Table 41 and Table 42. A single case may report more than 1 EOI.

Table 41: Serious MedDRA PTs of Interest and Their Outcomes in Post-marketing, Primary Dose Cases Reporting Vaccine Failure, Lack of Efficacy/Effectiveness With the Use of Ad26.COV2.S (Events=9,138)

MedDRA PTs	Number of Event Outcomes						
	Fatal	Not Resolved	Resolved	Resolved With Sequelae	Resolving	NR	Total Number of Events[a]
Vaccination failure	4	4	10	0	10	4,494	4,522
COVID-19	19	10	25	0	8	4,364	4,426

Table 41: Serious MedDRA PTs of Interest and Their Outcomes in Post-marketing, Primary Dose Cases Reporting Vaccine Failure, Lack of Efficacy/Effectiveness With the Use of Ad26.COV2.S (Events=9,138)

MedDRA PTs	Number of Event Outcomes						
	Fatal	Not Resolved	Resolved	Resolved With Sequelae	Resolving	NR	Total Number of Events[a]
SARS-CoV-2 test positive	15	9	21	1	4	10	60
Thrombosis with thrombocytopenia syndrome[b]	4	3	8	0	1	12	28
COVID-19 pneumonia	12	6	2	1	2	4	27
Suspected COVID-19	2	3	0	0	0	19	24
Drug ineffective	0	4	0	0	4	9	17
SARS-CoV-2 test negative	0	7	0	0	0	1	8

Key: COVID-19=Coronavirus Disease-2019; MedDRA=Medical Dictionary for Regulatory Activities; NR=Not Reported; PT=Preferred Term; SARS-CoV-2=Severe Acute Respiratory Syndrome Coronavirus-2

a: A single case may report more than 1 event of interest. The PTs having frequency ≥8 are presented.

b: Additional information included in Section 16.3.1.1, Thrombosis With Thrombocytopenia Syndrome.

Table 42: Nonserious MedDRA PTs of Interest and Their Outcomes in Post-marketing, Primary Dose Cases Reporting Vaccine Failure, Lack of Efficacy/Effectiveness With the Use of Ad26.COV2.S (Events=384)

MedDRA PTs	Number of Event Outcomes						
	Fatal	Not Resolved	Resolved	Resolved With Sequelae	Resolving	NR	Total Number of Events[a]
COVID-19	0	21	49	0	23	66	159
SARS-CoV-2 test positive	0	5	1	0	4	93	103
Suspected COVID-19	0	14	25	0	10	49	98
Asymptomatic COVID-19	0	1	5	0	0	1	7

Key: COVID-19=Coronavirus Disease-2019; MedDRA=Medical Dictionary for Regulatory Activities; NR=Not Reported; PT=Preferred Term; SARS-CoV-2=Severe Acute Respiratory Syndrome Coronavirus-2

a: A single case may report more than 1 event of interest. The PTs having frequency ≥7 are presented.

Fatal Post-marketing Primary Dose Cases

During the reporting interval, 49 initial, fatal cases were reported. Of these 49 fatal cases, 21 met the case definition of confirmed vaccination failure and 6 met the case definition of suspected vaccination failure (see Appendix 6.4). Overall, 51 EOI were reported in these 27 fatal cases during the interval. Of these 27 cases, 16 concerned males, 10 females, and 1 had no sex reported. The age range was 40 to 94 years. Among patients where age was reported, 1 was in the age range of 36 to 50 years, 6 were in the age range of 51 to 64 years, and 20 were ≥65 years.

The frequency distribution of the 51 MedDRA PTs of interest reported in these 27 cases is presented in Table 43 below. A single case may contain more than 1 EOI.

Table 43: Frequency Distribution of MedDRA PTs of Interest in Post-marketing Primary Dose Fatal Cases Involving the Use of Ad26.COV2.S and Reporting Vaccine Failure, Lack of Efficacy/Effectiveness (Events=51)

MedDRA PTs	Number of EOIs
COVID-19	19
SARS-CoV-2 test positive	15
COVID-19 pneumonia	10
Vaccination failure	5
Asymptomatic COVID-19	1
Post-acute COVID-19 syndrome	1
Total	**51**

Key: COVID-19=Coronavirus Disease-2019; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term; SARS-CoV-2=Severe Acute Respiratory Syndrome Coronavirus-2

Booster Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 418 (113 medically confirmed and 305 medically unconfirmed) post-marketing cases reported as booster were identified. There were 249 serious cases and 169 nonserious cases and reported a total of 674 EOI[20] (302 serious; 372 nonserious). Of these cases, 288 were heterologous and 130 were homologous.

Cumulatively, 667 (225 medically confirmed and 442 medically unconfirmed) post-marketing cases reported as booster were identified. Of these cases, 375 cases were serious and 292 were nonserious and reported a total of 1,060 EOI[20] (451 serious; 609 nonserious). Of these cases, 433 were heterologous and 234 were homologous.

Janssen Sponsored and Janssen Supported Clinical Studies (Booster Dose Cases)

Information on Janssen Sponsored and Janssen Supported Clinical Studies can be found in Section 13, Lack of Efficacy in Controlled Clinical Trials and Section 17, Benefit Evaluation of the PBRER.

Post-marketing Sources (Including Spontaneous and Solicited) Booster Dose Cases

An overview of the 418 (interval) and 667 (cumulative) post-marketing cases reporting booster dose is presented in Table 44 below.

[20] Fifteen cases for the current interval and 19 cases cumulatively reported events and the suspect product twice for patients receiving 2 doses of Ad26.COV.2.S. All events were conservatively included in the total event counts. Eighteen of these cases were received from Health Authorities and 1 was received from a Pregnancy Registry.

Table 44: Characteristics of Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Vaccine Failure, Lack of Efficacy/Effectiveness

Case Characteristics		Number of Cases Received During the Interval Reporting Period=418	Number of Cases Received Cumulatively=667
Sex	Female	214	304
	Male	145	228
	NR	59	135
Age (Years)[a]	18 to 35	76	130
Minimum: 19	36 to 50	110	167
Maximum: 96	51 to 64	106	158
Mean: 49.0	≥65	55	89
Median: 49	Adult	3	4
	Elderly	1	2
	NR	67	117
Sources	Spontaneous	380	621
	Clinical study (noninterventional, solicited)	24	32
	Clinical study (noninterventional, unsolicited)	14	14
Country/Territory[b]	United States	254	385
	Brazil	41	52
	Iceland	23	76
	Austria	20	21
	Germany	17	20
	Canada	16	21
	Spain	11	14
	France	8	12
	Belgium	4	10
	Denmark	4	5
	Lithuania	3	3
	Philippines	3	15
	Hungary	2	4
	Korea, Republic of	2	2
	Luxembourg	2	3
	Portugal	2	7
	South Africa	2	2
Event Characteristics		**Number of Events=674**	**Number of Events=1,060**
Seriousness Criteria (Event Level)[c, d]	Other medically important condition	274	378
	Hospitalisation	15	48
	Death	5	12
	Life-threatening	5	8
	Disability	3	5
	Nonserious	372	609
	Serious	302	451

Table 44: Characteristics of Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Vaccine Failure, Lack of Efficacy/Effectiveness

Case Characteristics		Number of Cases Received During the Interval Reporting Period=418	Number of Cases Received Cumulatively=667
Seriousness (Event Level)[c, d]	Nonserious	372	609
Outcome (Event Level)[c, d]	Not resolved	103	134
	Resolved	88	132
	Resolving	65	91
	Fatal	5	12
	Resolved with sequelae	1	1
	NR	412	690

Key: NR=Not Reported

a: The calculation was based on the current reporting period (25 February 2022 to 24 August 2022). Age group was presented for cases where age was not reported.

b: Countries/Territories are listed in descending frequency (≥2) for the current reporting period (25 February 2022 to 24 August 2022).

c: Seriousness criteria, seriousness and outcome have been presented for the events of interest. A single case may report more than 1 event of interest.

d: Fifteen cases for the current interval and 19 cases cumulatively reported events and the suspect product twice for patients receiving 2 doses of Ad26.COV.2.S. All events were conservatively included in the total event counts. Eighteen of these cases were received from Health Authorities and 1 was received from a Pregnancy Registry.

The frequency distribution of the MedDRA PTs of interest reported in post-marketing cases reported as booster is presented in Table 45 below. A single case may contain more than 1 EOI.

Table 45: Frequency of MedDRA PTs of Interest in Post-Marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Vaccine Failure, Lack of Efficacy/Effectiveness

MedDRA PTs	Number of Events Received During the Interval Reporting Period[a,b]		Number of Events Received Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
COVID-19	42	184	63	240
Vaccination failure	209	0	290	0
Suspected COVID-19	6	101	11	152
COVID-19 immunisation	9	36	18	87
SARS-CoV-2 test positive	3	38	8	108
Drug ineffective	14	0	17	0
COVID-19 pneumonia	8	0	12	0
Asymptomatic COVID-19	1	3	2	5
Therapy non-responder	4	0	18	0
Thrombosis with thrombocytopenia syndrome	4	0	4	0

Key: COVID-19=Coronavirus disease-2019; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term; SARS-CoV-2=Severe Acute Respiratory Syndrome Coronavirus-2

Table 45: Frequency of MedDRA PTs of Interest in Post-Marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Vaccine Failure, Lack of Efficacy/Effectiveness

MedDRA PTs	Number of Events Received During the Interval Reporting Period[a,b]		Number of Events Received Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious

a: The MedDRA PTs of interest with a frequency ≥4 have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event of interest.

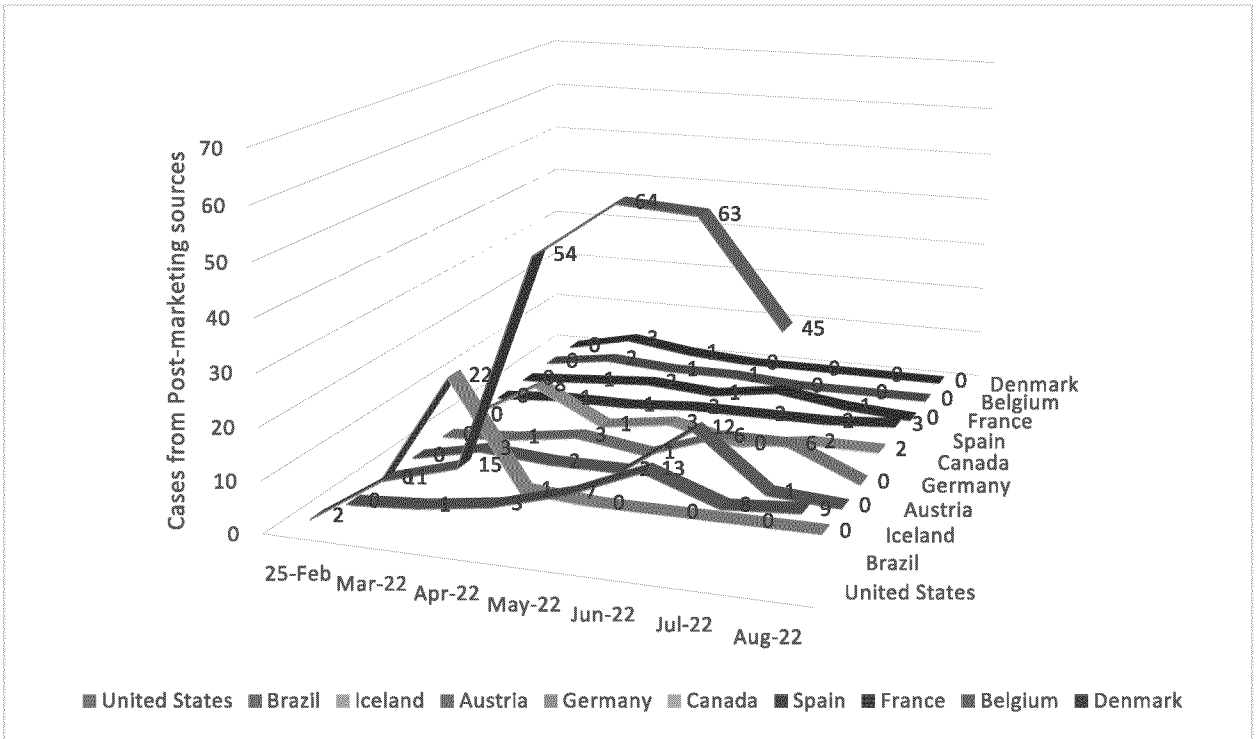
b: Fifteen cases for the current interval and 19 cases cumulatively reported events and the suspect product twice for patients receiving 2 doses of Ad26.COV.2.S. All events were conservatively included in the total event counts. Eighteen of these cases were received from Health Authorities and 1 was received from a Pregnancy Registry.

These 418 cases reported 302 serious EOI. Of these 418 cases, the most frequently reported country/territory of origin was the US (n=254). Of the 418 cases, 214 cases concerned females, 145 males, and 59 had no sex reported. The age range was 19 to 96 years.

The EOI (≥107) included COVID-19 (n=226), vaccination failure (n=209), and suspected COVID-19 (n=107). Where reported (n=262), the outcomes were not resolved (n=103), resolved (n=88), resolving (n=65), fatal (n=5), and resolved with sequelae (n=1).

Figure 3 below depicts the post-marketing (including spontaneous and solicited) cases reported as booster from the top 10 countries/territories by month.

Figure 3: Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Vaccine Failure, Lack of Efficacy/Effectiveness From the Top 10 Countries/Territories by Month



The TTO reported in these 418 cases is presented in Table 46.

Table 46: Time to Onset in Cases Reported as Booster Involving the Use of Ad26.COV2.S and Reporting Vaccine Failure, Lack of Efficacy/Effectiveness (Cases=418)

TTO	Number of Cases
≤14 days	10
>14 days but ≤28 days	14
>28 days	197
NR	197
Total[a]	**418**

Key: NR=Not Reported; PBRER=Periodic Benefit Risk Evaluation Report; TTO=Time to Onset
a: TTO categories have been presented at the case level in the current PBRER, as compared to the event level presented in the previous PBRER.

Laboratory findings reported are provided in Table 47 below.

Table 47: Laboratory Findings in Cases Reported as Booster Involving the Use of Ad26.COV2.S and Reporting Vaccine Failure, Lack of Efficacy/Effectiveness (Cases=418)

Laboratory Findings	Number of Cases
COVID-19 test positive	239
COVID-19 test negative	7
Antibody test negative	2
Antibody test positive	1
NR	169

Key: COVID-19=Coronavirus Disease-2019; n=Number of Cases; NR=Not Reported

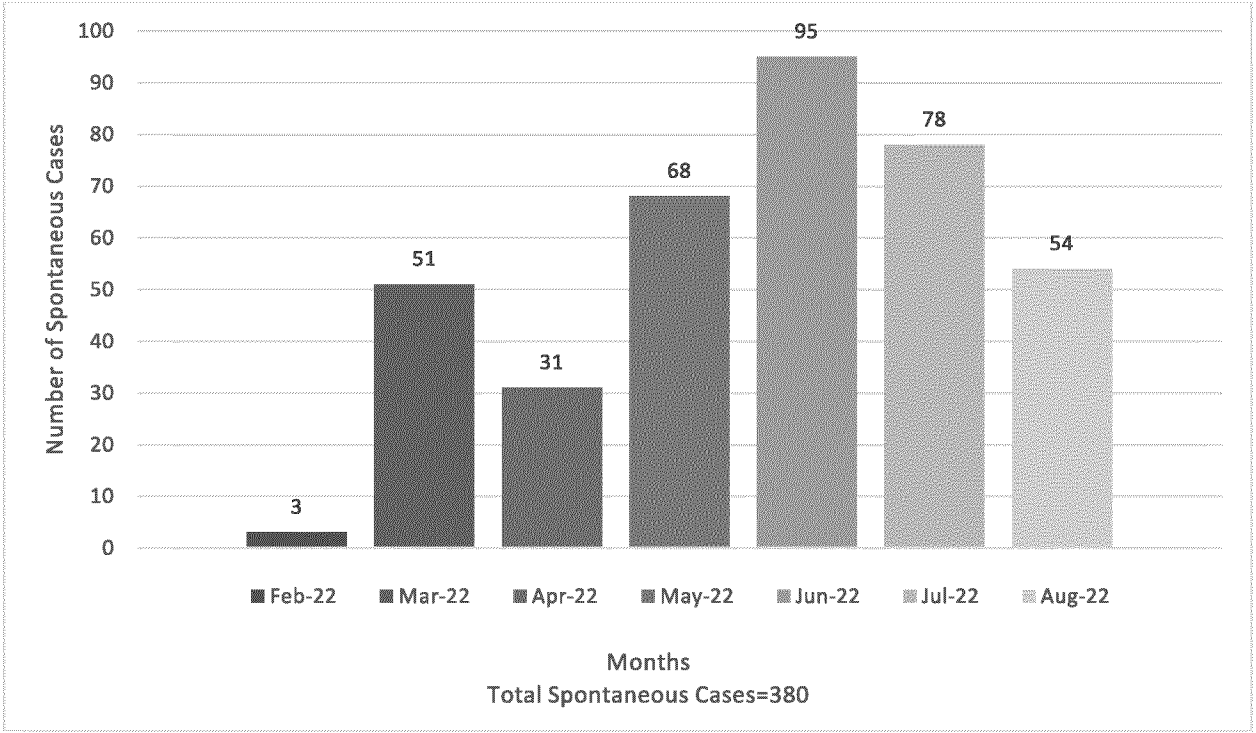
Of the 418 post-marketing cases reported as booster, 1 case reported the presence of the Omicron variant. This was a fatal heterologous case concerning a 96-years-old female patient with atrial fibrillation, dyslipidaemia, stroke, arterial hypertension, senile macular degeneration, cardiac failure, and haemorrhage of digestive tract as concurrent conditions. Concomitant medications included amiodarone hydrochloride, nicardipine hydrochloride, clopidogrel bisulfate, metopimazine and mirtazapine. The patient received their first dose of Ad26.COV2.S with no adverse events reported. The patient received booster vaccination with an mRNA vaccine, this was the second dose. Two hundred thirty-seven days after Ad26.COV2.S administration and 178 days after mRNA vaccine administration, the patient experienced COVID-19 pneumonitis confirmed by PCR testing (omicron variant with presence of the 417N mutation, and absence of the 484K and 452R mutations & absence of the 69-702 deletion) and CT scan bibasal endobronchial filling with pneumopathy focus downstream at the bases, and multiple stable vertebral fractures. The patient died of haemorrhagic shock, 292 days after Ad26.COV2.S and 233 days after mRNA vaccine. No reports of hypoxia or respiratory distress which make VAERD unlikely. This case is included in Fatal Post-marketing Booster Dose Fatal cases.

The Company case definition of vaccination failure is as follows: medically confirmed, TTO >14 days, and positive COVID-19 testing; 62 (21 homologous and 41 heterologous) of the 418 cases met this case definition. Additionally, 1 homologous case of the 418 cases also reported

suspected vaccination failure. In this case, TTO was greater than 14 days and medically confirmed; however, no laboratory test results were specified.

Figure 4 depicts the monthly post-marketing spontaneous case count (booster) from February 2022 to August 2022.

Figure 4: Case Count of Post-Marketing marketing Spontaneous Cases reported as Booster by Month Involving the Use of Ad26.COV2.S and Reporting Vaccine Failure, Lack of Efficacy/Effectiveness



The total 674 EOI are further sorted by seriousness and their respective outcomes in Table 48 and Table 49. A single case may report more than 1 EOI.

Table 48: Serious MedDRA PTs of Interest and Their Outcomes in Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Vaccine Failure, Lack of Efficacy/Effectiveness (Events=302)

MedDRA PTs	Number of Event Outcomes						
	Fatal	Not Resolved	Resolved	Resolved With Sequelae	Resolving	NR	Total Number of Events[a]
Vaccination failure	1	1	5	0	2	200	209
COVID-19	1	4	8	0	1	28	42
Drug ineffective	0	1	3	0	1	9	14
COVID-19 immunisation	1	3	1	0	1	3	9
COVID-19 pneumonia	2	1	2	0	1	2	8

Table 48: Serious MedDRA PTs of Interest and Their Outcomes in Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Vaccine Failure, Lack of Efficacy/Effectiveness (Events=302)

MedDRA PTs	Number of Event Outcomes						
	Fatal	Not Resolved	Resolved	Resolved With Sequelae	Resolving	NR	Total Number of Events[a]
Suspected COVID-19	0	1	2	0	0	3	6
Therapy non-responder	0	0	0	0	0	4	4
Thrombosis with thrombocytopenia syndrome[b]	0	0	3	0	0	1	4

Key: COVID-19=Coronavirus Disease-2019; MedDRA=Medical Dictionary for Regulatory Activities; NR=Not Reported; PT=Preferred Term

a: A single case may report more than 1 event of interest. The PTs with frequency ≥4 have been presented.

b: Additional information included in Section 16.3.1.1, Thrombosis With Thrombocytopenia Syndrome.

Table 49: Nonserious MedDRA PTs of Interest and Their Outcomes in Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Vaccine Failure, Lack of Efficacy/Effectiveness (Events=372)

MedDRA PTs	Number of Event Outcomes						
	Fatal	Not Resolved	Resolved	Resolved With Sequelae	Resolving	NR	Total Number of Events[a]
COVID-19	0	52	30	1	46	55	184
Suspected COVID-19	0	25	24	0	11	41	101
SARS-CoV-2 test positive	0	3	2	0	1	32	38
COVID-19 immunisation	0	4	4	0	1	27	36
Asymptomatic COVID-19	0	2	0	0	0	1	3

Key: COVID-19=Coronavirus Disease-2019; MedDRA=Medical Dictionary for Regulatory Activities; NR=Not Reported; PT=Preferred Term; SARS-CoV-2=Severe Acute Respiratory Syndrome Coronavirus-2

a: A single case may report more than 1 event of interest. The PTs with frequency ≥3 have been presented.

Fatal Post-marketing Booster Dose Cases

During the reporting interval, 6 fatal booster cases were reported. Of these 6 cases, 4 met the definition of confirmed vaccination failure (1 homologous and 3 heterologous) (see Appendix 6.4). Of the 4 fatal confirmed vaccination failure cases, 3 concerned males and 1 female. The age range reported in these 4 cases was 68 to 96 years.

The homologous confirmed vaccination failure fatal outcome case involved a 68-year-old incarcerated male with a medical history of cervical and supraspinal laminectomy and reported concurrent conditions of chronic pain, mobility issue, wheelchair use, ventilator use (not further

specified), obesity, sedation, high blood pressure, and chronic neck and back pain. Concomitant medications included paracetamol and influenza vaccine given within 4 weeks of symptom onset. At an unspecified time following Dose 1 of Ad26.COV2.S, the patient experienced sepsis (not further specified). Approximately 1 year following Dose 1- and 78-days following Dose 2 of Ad26.COV2.S, the patient experienced trouble breathing which increased over the next several days. The patient was reported to be refusing to come out of his cell for treatment and was eventually escorted to the clinic. On examination, the patient was noted to be hypoxic and oxygen saturation was reported as 78%. The patient was given supplemental oxygen and transported to the hospital where the patient was admitted for acute respiratory failure. PCR testing for COVID-19 was initially negative times 2, but the patient's condition worsened, and the patient was intubated and placed on a ventilator. The patient was found to have a right leg DVT, left pulmonary thrombosis, and acute respiratory distress syndrome. The patient was treated with anticoagulants. A third COVID-19 test was positive. A CT of the chest showed that the pulmonary embolism had resolved, but also showed patchy bilateral pneumonia which had worsened. A CT angiogram of the head showed a subdural haematoma; anticoagulation therapy was stopped. An intravenous catheter and gastrointestinal tube were placed, but the patient's condition continued to decline despite treatment with steroids, antibiotics, and fresh frozen plasma. The patient subsequently went into cardiac arrest from which the patient was resuscitated. Due to the patient's poor prognosis, the patient's family decided to not continue further resuscitative measures. The patient again went into cardiac arrest and died from acute respiratory distress syndrome (ARDS). VAERD cannot be ruled out due to the patient's documented ARDS. The patient's medical history of high blood pressure, obesity, mobility issues requiring wheelchair use, as well as social circumstances may have contributed to the severity of the patient's illness and subsequent fatal outcome.

The frequency distribution of the MedDRA PTs of interest reported in these 4 cases is presented in Table 50 below. A single case may contain more than 1 EOI.

Table 50: Frequency Distribution of MedDRA PTs of Interest in Cases Reported as Booster Involving the Use of Ad26.COV2.S and Reporting Vaccine Failure, Lack of Efficacy/Effectiveness (Events=7)

MedDRA PTs	Number of EOIs
COVID-19 pneumonia	3
Vaccination failure	3
COVID-19	1
Total	**7**

Key: EOI=Events of Interest; COVID-19=Coronavirus Disease-2019; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term

Literature ICSR

ICSR literature cases received during the reporting period of 25 February 2022 to 24 August 2022 were reviewed, and no information was identified that would change the characterisation of risk.

Discussion

Similarly, to the previous reporting period from 25 August 2021 to 24 February 2022, Austria continues to be the country with the highest number of cases, accounting for 87.8% of standard dose cases reported during the interval from 25 February 2022 to 24 August 2022. This increase continues to be related to proactive real-time surveillance by the Health Authority. All laboratories in Austria were obliged by law to report laboratory test results for all notifiable diseases in electronic form and without time lags to the epidemiologic reporting system Epidemiologisches Meldesystem (EMS). These cases from EMS were checked against the electronic vaccination certificate registry as EMS is a central public information system connected to all levels of Austrian health administration. This system is unique to Austria and explains the high reporting rate. The cases from Austria were received via line listings with minimal case data. However, no new cases received from Austria reported events that were fatal, life-threatening, required hospitalisation or were disabling.

During this reporting period, from 4,950 standard dose cases received, 4 cases reported variant sequencing of which one was fatal. From 418 booster dose cases, 1 reported Omicron variant after heterologous vaccination, this case was fatal. In both cases these patients presented conditions that could have contributed to the severity of COVID-19 disease.

In addition to the active surveillance activities, the Company continuously monitors incoming case reports of COVID-19 following vaccination with Ad26.COV2.S alongside cases of LOE/vaccination failure. As of now, no signal of LOE has been identified from post-authorisation sources. The Company will continue to monitor these case reports and discuss of efficacy/vaccination failure in upcoming periodic safety reports.

Conclusion

Based on the review of all the available data, no new significant safety information is observed in the review of vaccination failure cases. No signal suggestive of vaccine failure has been identified with Ad26.COV2.S. The Company will continue to monitor and present cases of vaccination failure in upcoming PBRERs.

15.6. Reactogenicity

Introduction

Reactogenicity is a standard topic for review in vaccine PBRERs. Reactogenicity is the physical manifestation of inflammatory response(s) to vaccination. These responses may include injection site pain, redness, swelling, or induration at the injection site. In addition, systemic symptoms may be observed such as fever, myalgia, or headache (Herve 2019).

Methods

The Company global safety database was searched for medically confirmed and medically unconfirmed cases received during this reporting period and cumulatively which coded to the search criteria provided in Appendix 5.

Reported events were further sorted into local reactogenicity versus systemic reactogenicity reactions. Local reactogenicity reactions included High Level Term (HLT) of Administration site reactions NEC, Injection site reactions, and Vaccination site reactions. Systemic reactogenicity reactions included PTs of Headache, Pyrexia, Myalgia, Arthralgia, Vomiting, Diarrhoea, Paraesthesia, Hypoaesthesia, Dizziness, Chills, Fatigue, Asthenia, Muscular weakness, and Pain in extremity.

An additional manual review of the cases was performed with a reported latency period maximum of 1 week and only if leading to hospitalisation or considered life threatening.

Results/Discussion

Primary Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 211 (64 medically confirmed and 147 medically unconfirmed) initial, primary dose cases reporting reactogenicity were identified. All of the cases were serious and reported a total of 702 serious EOI.

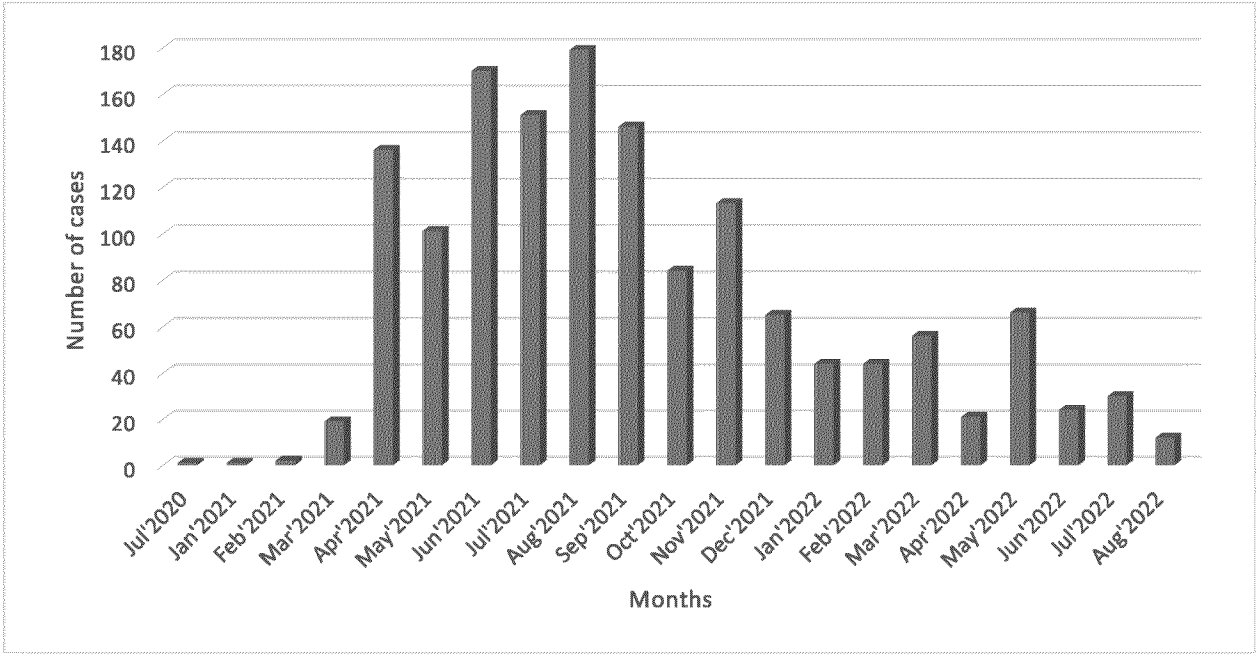
All 211 primary dose cases received during the interval reporting period were reported from post-marketing sources (including spontaneous and solicited). No cases were reported from Janssen Sponsored Clinical Studies or Janssen Supported Clinical Studies.

Cumulatively, 1,465 (670 medically confirmed and 795 medically unconfirmed) primary dose cases reporting reactogenicity were identified. All of the cases were serious and reported a total of 3,495 serious EOI.

Of the 1,465 cumulative primary dose cases received, 6 were reported from Janssen Sponsored Clinical Studies, 8 from Janssen Supported Clinical Studies, and 1,451 from post-marketing sources (including spontaneous and solicited cases).

Figure 5 depicts the cumulative number of cases (n=1,465) month-wise.

Figure 5: Cumulative Case Reports by Month



Janssen Sponsored and Janssen Supported Clinical Studies (Primary Dose Cases)

There were no initial, primary dose cases retrieved from the search of the Company global safety database during the reporting period of 25 February 2022 to 24 August 2022 for either the Janssen Sponsored or Janssen Supported Clinical Studies.

Post-marketing Sources (Including Spontaneous and Solicited) Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 211 post-marketing sources (including spontaneous and solicited), initial, primary dose cases reporting reactogenicity were retrieved. These 211 post-marketing, initial, primary dose cases reported 702 serious EOI.

Cumulatively, 1,451 (656 medically confirmed and 795 medically unconfirmed) post-marketing, primary dose cases reporting reactogenicity were identified. These 1,451 post-marketing, primary dose cases reported 3,476 serious EOI.

An overview of these cases is presented in Table 51 below.

Table 51: Characteristics of Post-marketing, Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Reactogenicity

Case Characteristics		Number of Cases Received During the Interval Reporting Period=211	Number of Cases Received Cumulatively=1,451
Sex	Female	102	789
	Male	96	645
	NR	13	17
Age (Years)[a]	<18	0	3
Minimum: 18	18 to 35	99	445
Maximum: 82	36 to 50	67	473
Mean: 38.6	51 to 64	31	336
Median: 36	≥65	11	166
	Adult	1	5
	NR	2	23
Sources	Spontaneous	182	1,396
	Clinical study (noninterventional; solicited)	29	55
Country/Territory[b]	Germany	89	280
	South Africa	45	56
	United States	20	463
	Greece	15	36
	Poland	15	21
	Philippines	10	73
	Austria	4	34
	Latvia	3	17
Event Characteristics		**Number of Events=702**	**Number of Events=3,476**
Seriousness (Event Level)[c]	Serious	702	3,476
Outcome (Event Level)[c]	Not resolved	274	1,237
	Resolving	260	750
	Resolved	88	701
	Resolved with sequelae	33	98
	Fatal	5	71
	NR	42	619

Key: NR=Not Reported

a: The calculation was based on the current reporting period (25 February 2022 to 24 August 2022). Age group was presented for cases where age was not reported.

b: Countries/Territories with frequency ≥3 were presented in decreasing order for the current reporting period (25 February 2022 to 24 August 2022).

c: Seriousness and outcome have been presented for the events of interest. A single case may report more than 1 event of interest.

Of these 211 post-marketing, initial, primary dose cases, the most frequently reported countries/territories of origin (n≥20) were Germany (n=89), followed by South Africa (n=45) and

the US (n=20). These cases concerned 96 males, 102 females, and 13 did not report sex. The age range was from 18 to 82 years.

Local Reactogenicity Reactions

Thirty-four post-marketing primary dose cases reported local reactogenicity reactions. The reported countries/territories of origin were Germany (n=24), Philippines (n=4), South Africa (n=3), Greece (n=2), and Poland (n=1). These cases concerned 17 males, 15 females, and 2 did not report sex. The age range was from 18 to 63 years.

The frequency distribution of the MedDRA PTs of interest reported in post-marketing, primary dose cases is presented in Table 52 below. The event outcomes are presented in Table 53. A single case may report more than 1 EOI.

Table 52: Frequency of MedDRA PTs of Interest in Post-marketing, Primary Dose Cases Reporting Local Reactogenicity Reactions With the Use of Ad26.COV2.S

MedDRA PTs	Number of Serious Events Received During Reporting Period[a]	Number of Serious Events Received Cumulatively
Injection site pain	53	127
Injection site swelling	9	27
Vaccination site pain	7	18
Vaccination site reaction	3	4
Injection site bruising	2	3
Injection site erythema	1	10

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: The MedDRA PTs of interest were sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022).

Table 53: Frequency of MedDRA PTs of Interest in Post-marketing, Primary Dose Cases and Their Outcomes for Local Reactogenicity Reactions With the Use of Ad26.COV2.S

MedDRA PTs	Number of Event Outcomes				
	Not Resolved	Resolved	Resolving	NR	Total Number of Serious Events
Injection site pain	14	8	29	2	53
Injection site swelling	3	1	5	0	9
Vaccination site pain	3	0	4	0	7
Vaccination site reaction	1	0	0	2	3
Injection site bruising	0	1	1	0	2
Injection site erythema	0	0	0	1	1
Total Events	**21**	**10**	**39**	**5**	**75**

Key: MedDRA=Medical Dictionary for Regulatory Activities; NR=Not Reported; PT=Preferred Term

The most frequently reported EOI (n≥9) were injection site pain (n=53) and injection site swelling (n=9). The mean and median TTO were 0.7 day and same day, respectively. Where reported (n=70), the outcomes were resolving (n=39), not resolved (n=21), and resolved (n=10).

Additionally, cases were reviewed to determine if there were any reported important identified (eg, TTS), or important potential risks (eg ITP). Of these 34 cases, venous thromboembolism ([VTE) (n=1)] was reported.

Systemic Reactogenicity Reactions

Two-hundred and five post-marketing primary dose cases reported systemic reactogenicity reactions. The most frequently reported countries/territories of origin (n≥15) were Germany (n=87), South Africa (n=45), US (n=20), and Poland and Greece (n=15 each). These cases concerned 93 males, 100 females, and 12 did not report sex. The age range was from 18 to 82 years.

The frequency distribution of the MedDRA PTs of interest reported in post-marketing, primary dose cases is presented in Table 54 below. The event outcomes are presented in Table 55. A single case may report more than 1 EOI.

Table 54: Frequency of MedDRA PTs of Interest Reported in Post-marketing, Primary Cases Reporting Systemic Reactogenicity With the Use of Ad26.COV2.S

MedDRA PTs	Number of Serious Events Received During Reporting Period[a]	Number of Serious Events Received Cumulatively
Headache	119	565
Fatigue	107	368
Dizziness	76	369
Pyrexia	66	417
Myalgia	50	233
Arthralgia	35	143
Paraesthesia	34	153
Chills	30	241
Hypoaesthesia	24	156
Pain in extremity	20	164
Asthenia	19	150
Diarrhoea	18	83
Vomiting	17	131
Muscular weakness	12	71

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: The MedDRA PTs of interest were sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022).

Table 55: Frequency Distribution of MedDRA PTs of Interest Reported in Post-marketing, Primary Cases and Outcomes for Systemic Reactogenicity Reactions With Ad26.CoV2.S

MedDRA PTs	Number of Event Outcomes						
	Fatal	Not Resolved	Resolved	Resolved With Sequelae	Resolving	NR	Total Number of Serious Events
Headache	0	51	17	5	39	7	119
Fatigue	0	50	9	5	37	6	107
Dizziness	0	26	10	7	29	4	76
Pyrexia	1	21	12	6	21	5	66
Myalgia	0	24	0	2	21	3	50
Arthralgia	0	18	2	1	12	2	35
Paraesthesia	0	13	0	5	16	0	34
Chills	1	6	7	0	14	2	30
Hypoaesthesia	0	9	5	2	7	1	24
Pain in extremity	0	15	1	0	3	1	20
Asthenia	2	7	6	0	4	0	19
Diarrhoea	0	5	4	0	7	2	18
Vomiting	1	3	4	0	6	3	17
Muscular weakness	0	5	1	0	5	1	12
Total Events	**5**	**253**	**78**	**33**	**221**	**37**	**627**

Key: MedDRA=Medical Dictionary for Regulatory Activities; n=Number; NR=Not Reported; PT=Preferred Term

The most frequently reported EOI (n≥107) were headache (n=119) and fatigue (n=107). The mean and median TTO were 1.4 days and 1 day, respectively. Where reported (n=590), the outcomes were not resolved (n=253), resolving (n=221), resolved (n=78), resolved with sequelae (n=33), and fatal (n=5). There were 3 fatal cases reporting 5 fatal EOI. The reported EOI with a fatal outcome were asthenia (n=2), and vomiting, chills, and pyrexia (n= 1 each). The review of these cases did not reveal any new safety information.

Additionally, cases were reviewed to determine if there were any reported important identified (eg, TTS), or important potential risks (eg, ITP). Of these 205 cases, Guillain-Barré syndrome ([GBS (n=1)], VTE (n=17), TTS (n=1), and ITP (n=1) were reported.

Fatal Post-marketing Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 3 post-marketing, initial, primary dose fatal cases with 5 fatal EOI were retrieved. The fatal EOI were asthenia (n=2), and vomiting, chills, and pyrexia (n= 1 each). The first case from the US concerned a 28-year-old male with an unknown medical history who experienced flushing, malaise, asthenia, and a burning sensation 1 day following vaccination with Ad26.COV2.S. Subsequently, the patient was diagnosed with type I diabetes mellitus and was hospitalised for diabetic ketoacidosis. Approximately 354 days following vaccination with Ad26.COV2.S, the patient died. The cause of death was not reported. It was unknown if an autopsy was reported. The second case from South Africa concerned a 24-year-old male with an unknown medical history who experienced weakness and a generalised convulsion 1 day following vaccination with Ad26.COV2.S. Subsequently, the

patient was hospitalised and died. It was reported that the fatal outcome occurred approximately 3 days following vaccination with Ad26.COV2.S. It was unknown if an autopsy was performed. The third case from the US concerned a 71-year-old male with concurrent conditions of a diabetes mellitus, renal stones, and chronic urinary tract infections, and was hospitalised 2 days following vaccination with Ad26.COV2.S secondary to fever, vomiting, and chills. The patient was diagnosed with septic shock, liver failure, renal failure, and thrombosis. It was reported that the patient was treated with myocardial infarction drugs for hypotension. Forty-six days following vaccination with Ad26.COV2.S, the patient died from hepatic failure, chills, pyrexia, renal failure, septic shock, thrombosis, hypotension, and vomiting. It was unknown if an autopsy was performed.

Booster Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 29 (6 medically confirmed and 23 medically unconfirmed) initial cases reported as booster were identified. All of the cases were serious and reported a total of 69 serious EOI. Of these cases, 21 were heterologous and 8 were homologous.

All 29 primary dose cases received during the interval reporting period were reported from post-marketing sources (including spontaneous and solicited). No cases were reported from Janssen Sponsored Clinical Studies or Janssen Supported Clinical Studies.

Cumulatively, 53 (15 medically confirmed and 38 medically unconfirmed) cases reported as booster were identified. All of the cases were serious and reported a total of 121 serious events. Of these cases, 32 were heterologous and 21 were homologous.

Cumulatively, all 53 booster cases were reported from post-marketing sources (including spontaneous and solicited). No cases were reported from Janssen Sponsored Clinical Studies or Janssen Supported Clinical Studies.

A cumulative booster dose CIOMS II LL is presented in Appendix 6.5.

Janssen Sponsored and Janssen Supported Clinical Studies (Booster Dose Cases)

There were no initial cases reported as booster which were retrieved from the search of the Company global safety database during the interval reporting period of 25 February 2022 to 24 August 2022 for either the Janssen Sponsored or Janssen Supported Clinical Studies.

Post-marketing Sources (Including Spontaneous and Solicited) Booster Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 29 post-marketing sources (including spontaneous and solicited), initial cases reported as booster were retrieved. These 29 post-marketing booster dose cases reported 77 serious EOI.

Cumulatively, 53 (15 medically confirmed and 38 medically unconfirmed) post-marketing cases reported as booster were identified. All of the cases were serious and reported a total of 128 serious EOI.

An overview of these cases is presented in Table 56 below.

Table 56: Characteristics of Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Reactogenicity

Case Characteristics		Number of Cases Received During the Interval Reporting Period=29	Number of Cases Received Cumulatively=53
Sex	Female	16	31
	Male	13	22
Age (Years)[a]	<18	1	1
Minimum: 13	18 to 35	9	14
Maximum: 88	36 to 50	4	11
Mean: 46.5	51 to 64	10	21
Median: 48	≥65	3	4
	Adult	1	1
	NR	1	1
Country/Territory[b]	Germany	18	20
	Brazil	3	4
	South Africa	3	3
	Philippines	3	4
	Greece	1	2
	United States	1	14
Sources	Spontaneous	26	48
	Clinical study (noninterventional; solicited)	2	4
	Clinical study (noninterventional; unsolicited)	1	1
Classification	Heterologous	21	32
	Homologous	8	21
Event Characteristics		**Number of Events=77**	**Number of Events=128**
Seriousness (Event Level)[c]	Serious	77	128
Outcome (Event Level)[c]	Not resolved	38	58
	Resolving	13	16
	Resolved with sequelae	11	12
	Resolved	8	28
	Fatal	1	1
	NR	6	13

Key: NR=Not Reported

a: The calculation was based on the current reporting period (25 February 2022 to 24 August 2022). Age group was presented for cases where age was not reported.

b: Countries/Territories were presented in decreasing order for the current reporting period (25 February 2022 to 24 August 2022).

Table 56: Characteristics of Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Reactogenicity

Case Characteristics	Number of Cases Received During the Interval Reporting Period=29	Number of Cases Received Cumulatively=53

c: Seriousness and outcome have been presented for the events of interest. A single case may report more than 1 event of interest.

Of these 29 post-marketing, initial cases reported as booster, the most frequently reported countries/territories of origin (n≥3) were Germany (n=18), and Brazil, South Africa, and Philippines (n=3 each). These cases concerned 13 males and 16 females. The age range was from 13 to 88 years.

Local Reactogenicity Reactions

Four post-marketing booster cases reported local reactogenicity reactions. The reported countries/territories of origin were Germany (n=3) and Greece (n=1). These 4 cases concerned females with the age range from 34 to 71 years.

The frequency distribution of the MedDRA PTs of interest reported in post-marketing booster cases reporting local reactogenicity reactions is presented in Table 57 below. The event outcomes are presented in Table 58. A single case may report more than 1 EOI.

Table 57: Frequency of MedDRA PTs of Interest in Post-marketing Cases Reported as Booster Reporting Local Reactogenicity Reactions With the Use of Ad26.COV2.S

MedDRA PTs	Number of Serious Events Received During Reporting Period[a]	Number of Serious Events Received Cumulatively
Injection site pain	2	3
Injection site joint discomfort	1	1
Vaccination site pain	1	2
Injection site erythema	1	2

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term.
a: The MedDRA PTs of interest were sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022).

Table 58: Frequency Distribution of MedDRA PTs of Interest and Their Outcomes for Local Reactogenicity Reactions in Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S

MedDRA PTs	Number of Event Outcomes				
	Not Resolved	Resolved	Resolving	NR	Total Number of Serious Events
Injection site pain	0	1	1	0	2

Table 58: Frequency Distribution of MedDRA PTs of Interest and Their Outcomes for Local Reactogenicity Reactions in Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S

MedDRA PTs	Number of Event Outcomes				
	Not Resolved	Resolved	Resolving	NR	Total Number of Serious Events
Vaccination site pain	0	0	0	1	1
Injection site erythema	1	0	0	0	1
Injection site joint discomfort	0	0	1	0	1
Total Events	**1**	**1**	**2**	**1**	**5**

Key: MedDRA=Medical Dictionary for Regulatory Activities; NR=Not Reported; PT=Preferred Term

The reported EOI were injection site pain (n=2), vaccination site pain, injection site erythema. and injection site joint discomfort (n=1 each). The mean and median TTO were 1.2 days and same day, respectively. Where reported (n=4), the outcomes were resolving (n=2), not resolved (n=1), and resolved (n=1).

Additionally, cases were reviewed to determine if there were any reported important identified (eg, TTS), or important potential risks (eg, ITP). None of these cases reported any important identified or important potential risks.

Systemic Reactogenicity Reactions

Twenty-nine post-marketing booster cases reported systemic reactogenicity reactions. The most frequently reported countries/territories of origin (n≥3) were Germany (n=18),and Brazil, South Africa, and Philippines (n=3 each). These cases concerned 13 males and 16 females. The age range was from 13 to 88 years.

The frequency distribution of the MedDRA PTs of interest reported in post-marketing, primary dose cases is presented in Table 59 below. The event outcomes are presented in Table 60. A single case may report more than 1 EOI.

Table 59: Frequency Distribution of MedDRA PTs of Interest Reported in Post-marketing Primary Cases Reporting Systemic Reactogenicity Reactions With the Use of Ad26.COV2.S

MedDRA PTs	Number of Serious Events Received During Reporting Period[a]	Number of Serious Events Received Cumulatively
Fatigue	16	23
Headache	15	24
Dizziness	7	9
Pyrexia	6	11
Arthralgia	5	7
Chills	5	6
Myalgia	4	5
Vomiting	4	7
Hypoaesthesia	4	7

Table 59: Frequency Distribution of MedDRA PTs of Interest Reported in Post-marketing Primary Cases Reporting Systemic Reactogenicity Reactions With the Use of Ad26.COV2.S

MedDRA PTs	Number of Serious Events Received During Reporting Period[a]	Number of Serious Events Received Cumulatively
Pain in extremity	3	8
Diarrhoea	2	3
Paraesthesia	1	4

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: The MedDRA PTs of interest were sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022).

Table 60: Frequency Distribution of MedDRA PTs of Interest and Their Outcomes for Systemic Reactogenicity Reactions in Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S

MedDRA PTs	Number of Event Outcomes						
	Fatal	Not Resolved	Resolved	Resolved With Sequelae	Resolving	NR	Total Number of Serious Events
Fatigue	0	12	0	2	1	1	16
Headache	0	7	3	2	1	2	15
Dizziness	0	3	0	3	1	0	7
Pyrexia	0	2	3	0	1	0	6
Chills	1	1	0	0	2	1	5
Arthralgia	0	2	0	1	2	0	5
Myalgia	0	2	0	0	2	0	4
Vomiting	0	3	0	1	0	0	4
Pain in extremity	0	1	0	1	1	1	4
Hypoaesthesia	0	1	1	1	0	0	3
Diarrhoea	0	2	0	0	0	0	2
Paraesthesia	0	1	0	0	0	0	1
Total events	**1**	**37**	**7**	**11**	**11**	**5**	**72**

Key: MedDRA=Medical Dictionary for Regulatory Activities; n=Number; NR=Not Reported; PT=Preferred Term.

The most frequently reported EOI (n≥4) were fatigue (n=16), headache (n=15), dizziness (n=7), pyrexia (n=6), chills and arthralgia (n=5 each), and myalgia, vomiting, and pain in extremity (n=4 each). The mean and median TTO were 2.3 days and 1 day, respectively. Where reported (n=67), the outcomes were not resolved (n=37), resolved with sequelae (n=11), resolving (n=11), resolved (n=7), and fatal (n=1). The reported event with a fatal outcome was chills. The review of this case did not reveal any new safety information.

Additionally, cases were reviewed to determine if there were any reported important identified (eg. TTS), or important potential risks (eg. ITP). None of these cases reported any important identified or important potential risks.

Fatal Post-marketing Booster Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 1 fatal case reported as booster with 1 fatal EOI was retrieved. The fatal EOI was chills. This case from the Philippines concerned a 73-year-old male with a history of hypertension and a mild stroke who experienced malaise, fever, and chills approximately 1 day following a booster dose of COVID-19 vaccine (non-Company) and 301 days following Ad26.COV2.S vaccine. Subsequently, 3 days later, the patient was hospitalised due to a decreased appetite, abdominal pain, fever, and weakness. The patient was diagnosed with acute gastritis, chronic gouty arthritis, and prostate enlargement. Subsequently, the patient died due to malaise, joint pain, fever, chills, decreased appetite, and abdominal pain 6 days after admission. It was unknown if an autopsy was performed.

Literature ICSR

ICSR literature cases received during the reporting period of 25 February 2022 to 24 August 2022 were reviewed, and no information was identified that would change the characterisation of risk.

Conclusion

Local and systemic reactogenicity symptoms are included in the CCDS as common adverse reactions. The review of the cases received during the reporting period have not shown any changes in terms of severity or outcome warranting changes to the prescribing information (PI). No signal of vaccination anxiety-related reactions has been identified with Ad26.COV2.S.

16. SIGNAL AND RISK EVALUATION

16.1. Summary of Safety Concerns

16.1.1. At the Beginning of the Reporting Period

The summary of safety concerns (ie, important identified risks, important potential risks, and missing information) at the beginning of the reporting period to be included in the Ad26.COV2.S PBRER are based on cRMP (version 4.0 dated 09 December 2021) and are summarised in Table 61.

In addition, the summary safety concerns are also based on the following:

- important risk and missing information definitions provided in the ICH E2C guidelines on the PBRER and GVP Module VII - Periodic Safety Update Report.
- any additional safety concerns per other regional or country/territory-specific RMP requirements, as applicable.
- European Union (EU) RMP: version 2.5 (dated 02 December 2021).
  - Immune thrombocytopenia was reclassified as an important identified risk.

Of note, immune thrombocytopenia is presented within this PBRER under the important potential risk section as per the cRMP. This risk is comparable to thrombocytopenia, including ITP in the European Union Risk Management Plan.

- EU RMP: version 3.1 (dated 13 January 2022)
  - Venous thromboembolism was reclassified as an important identified risk.
- European Medicines Agency (EMA) core PSUR 19 guidance (EMA/362988/2021 dated 08 July 2021).

Note that the list of safety concerns in the EU RMP and/or cRMP may not be the same as the PBRER based on GVP Module V - Risk Management Systems (Revision 2).

Table 61: Important Identified Risks, Important Potential Risks and Missing Information at the Beginning of the Reporting Period in the Core Risk Management Plan

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[a] Immune thrombocytopenia[b]
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

Key: cRMP=Core Risk Management Plan; ITP=Immune thrombocytopenia
a: Venous thromboembolism has been reclassified as an important identified risk. The cRMP is in the process of being updated to reflect the reclassification.
b: ITP is comparable to thrombocytopenia, including ITP in the European Risk Management Plan.

16.1.2. At the End of the Reporting Period

During the reporting period, the safety concerns were re-evaluated. The updated summary of safety concerns which was based on the cRMP is presented below in Table 62.

- The cRMP version 4.0 was updated to version 5.0 on 24 May 2022 with the removal of the safety concern of Anaphylaxis which was previously classified as an important identified risk. This update is discussed under the appropriate subsection in Section 16.3.
- European Union RMP: version 4.2 (dated 07 July 2022):
  - For Anaphylaxis, as per the PRAC FAR for the Ad26.COV2.S PBRER (EMEA/H/C/PSUSA/00010916/202108) received on 10 March 2022, MAH was requested to reclassify "Anaphylaxis" as not "important", and requested to remove it from the summary of safety concerns in the RMP at the next regulatory opportunity. EMA endorsed removal of Anaphylaxis in version 4.2 of the EU RMP (CHMP opinion on 07 July 2022) and it was removed in the subsequent cRMP (version 5.0; dated 24 May 2022).

Table 62: Important Identified Risks, Important Potential Risks and Missing Information at the End of the Reporting Period in the Core Risk Management Plan

Important Identified Risks	Thrombosis with thrombocytopenia syndrome Guillain-Barré syndrome
Important Potential Risks	Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) Venous thromboembolism[a] Immune thrombocytopenia[b]
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

Key: cRMP=Core Risk Management Plan; ITP=Immune thrombocytopenia

a: Venous thromboembolism has been reclassified as an important identified risk. The cRMP is in the process of being updated to reflect the reclassification.

b: ITP is comparable to thrombocytopenia, including ITP in the European Risk Management Plan.

16.2. Signal Evaluation

16.2.1. Closed Signals

This section presents those signals which were closed within the STS, following the PBRER ICH E2C guidelines and Module VII of the GVP. This represents that the evaluation and review process has been completed. Depending on the outcome of the evaluation, these signals may continue to be monitored by regular pharmacovigilance (PV) activities or closely monitored and discussed in future PBRERs/PSURs.

16.2.1.1. Closed and Refuted Signals

During the reporting period, the following signals were closed but with continued routine pharmacovigilance (see Appendix 3).

16.2.1.1.1. IgA Nephropathy

Request: On 22 February 2022, the Company received a request from the WHO Uppsala Monitoring Centre:

"*to comment on a safety signal for IgA nephropathy following administration of COVID-19 vaccines, which was detected during screening of the WHO safety database VigiBase on 21 April 2021. The health authorities mentioned that as of 31 October 2021, 64 cases reporting IgA nephropathy following COVID-19 vaccination underwent manual clinical evaluation. The majority of cases followed administration of an mRNA based COVID-19 vaccine. The WHO Uppsala Monitoring Center invited Janssen to comment on this signal by the date of 07 March 2022.*"

Conclusion: Based on the review of evidence from cases from interventional clinical studies and post-marketing surveillance data, there is no evidence of an association between the event of IgA nephropathy and vaccination with Ad26.COV2. S. vaccine.

Additional information on this analysis can be found in Section 8, Overview of Signals, in the bimonthly Summary Safety Report dated 16 January 2022 to 15 March 2022.

16.2.1.1.2. Facial Paralysis

Request: During the generation of the previous PBRER dated 25 August 2021 to 24 February 2022, a pooled analysis of the double-blind phases of 5 Company-sponsored trials showed a numerical imbalance for facial paralysis between Ad26.COV2.S and placebo. An analysis was conducted on all available data.

Conclusion: Overall, these data support a revision to the Ad26.COV2.S Product Information to include facial paralysis (including Bell's palsy) with a frequency of "rare". The Company added facial paralysis including Bell's Palsy as an ADR. The Company will continue to monitor cases of facial paralysis (including Bell's palsy) through routine pharmacovigilance activities.

Additional information can be found in Section 2.1 of the Response document titled: Response to the PRAC Rapporteur's Preliminary Assessment Report: Periodic Safety Update Report (Reporting Period: 25 August 2021 to 24 February 2022) JCOVDEN Procedure Number: EMEA/H/C/PSUSA/00010916/202202 (dated 26 August 2022). PRAC has endorsed the Company's updates.

16.2.1.1.3. Coronary Artery Disease, including Myocardial Infarction

Request: On 08 March 2022, the Company received the PRAC FAR for the ninth SSR, which requested a legally binding measure (LEG) for Ad26.COV2.S to include an in-depth review of CAD including AMI; a discussion of the French EPI-PHARE epidemiological study that indicated a slight increased risk of myocardial infarction (MI) in the first 2 weeks following vaccination with Ad26.COV2.S; and a cumulative review of CAD (including AMI) cases, based on data from clinical trials, post-marketing data and literature, including (age) stratified O/E analyses.

Conclusion: Based on review of all available data, the weight of cumulative evidence is insufficient to support a causal association between CAD (including AMI) and the Ad26.COV2.S vaccine.

Key factors supporting this conclusion include lack of established biological plausibility, no increased risk observed from review of a large clinical trial dataset, and insufficient evidence from the biomedical literature, clinical trials, and aggregate post-marketing spontaneous reports as well as RWE to support a causal relationship between the development of CAD (including AMI) and Ad26.COV2.S. The Company will continue to monitor events of CAD (including AMI) via routine PV activities.

Additional information on the analysis can be found in Appendix 9.5 and also in Section 16.3.6.1.3, Coronary artery disease, including Myocardial Infarction below.

16.2.1.2. Closed Signals That are Categorised as Important Identified Risks

16.2.1.2.1. Venous Thromboembolism

Request: During the reporting period of the bimonthly SSR (16 March 2022 to 15 May 2022), the Company conducted an updated review of VTE.

Conclusion: After the review of the data from different sources (pooled safety data from clinical trials, literature, O/E, real world data [RWD] analysis and post-marking reporting), the Company considered that there is sufficient evidence of a causal relationship between Ad26.COV.2.S vaccination and the occurrence of venous thromboembolism. Consequently, the CCDS and the cRMP will be updated to add venous thromboembolism as an ADR and an important identified risk respectively.

Additional information on this analysis can be found in Section 8.4, Overview of Signals in the bimonthly SSR dated 16 March 2022 to 15 May 2022 and in Section 16.3.1.3, Venous thromboembolism below.

Venous thromboembolism has been reclassified as an important identified risk in the EU RMP. The cRMP is in the process of being updated to reflect the reclassification.

16.2.1.3. Closed Signals That are Categorised as Important Potential Risks

There were no closed signals were categorised as important potential risks.

16.2.1.4. Closed Signals That are Identified Risks not Categorised as Important

There were no closed signals that were categorised as identified risks not categorised as important.

16.2.1.5. Closed Signals That are Potential Risks not Categorised as Important

There were no closed signals that were categorised as potential risks not categorised as important.

16.3. Evaluation of Risks and New Information

Effectiveness of Targeted Follow-up Questionnaires

In alignment with EU GVP Module V, the Company has implemented specific follow-up questionnaires for certain events of special interest as part of its routine pharmacovigilance activities. During the reporting period, the following Targeted Follow-up Questionnaires (TFUQs) were used by the Company for Ad26.COV2.S post-marketing surveillance:

Safety Concern/Event of Interest	Purpose/Description
Thrombosis with thrombocytopenia syndrome Venous thromboembolism	TFUQ for the characterization of venous thromboembolism and thrombosis with thrombocytopenia syndrome.
Vaccine-associated enhanced disease, including VAERD	TFUQ to collect information on vaccination failure/lack of effect, including events of VAED and VAERD.
Multisystemic Inflammatory Syndrome	TFUQ to collect information on MIS in Adults (MIS-C), Currently the Company has no paediatric indication for Ad26.COV2.S.

Key: MIS=Multisystemic Inflammatory Syndrome; TFUQ=Targeted Follow-up Questionnaires; VAED=Vaccine-associated Enhanced Disease; VAERD=Vaccine-associated Enhanced Respiratory Disease

Results

During the reporting period, the Company issued at least 1 TFUQ for 247 cases in the US, of which 47 had a reply received by the Company. Cumulatively since launch, the Company has issued at least 1 TFUQ for 2,062 cases in the US, of which 231 had a reply received by the Company (this includes questionnaires for the topic of Anaphylaxis, no longer followed up using TFUQ).

In the EEA and Rest of World (ROW), the issuing of TFUQs is carried out by each Local Operating Company; therefore, the Company has no centralised process for the collection of issued/answered TFUQs.

Conclusion

Overall, response rates from targeted questionnaires have been consistently low. This is in line with the general experience from the Company in the issuing of TFUQs.

Given the very low usage of the vaccine in both the US and EEA, in addition to the relatively low response rates, the Company proposes the retirement of the 3 currently active TFUQs, and to continue to monitor the conditions of interest through their associated PV activities (for TTS/VTE and VAED/VAERD) and routine PV activities (MIS).

16.3.1. New Information on Important Identified Risks

Anaphylaxis has been removed from both the cRMP (version 5.0) and from the EU RMP (version 4.2).

16.3.1.1. Thrombosis With Thrombocytopenia Syndrome

Introduction

According to the cRMP (version 4.0; dated 09 December 2021), TTS is an important identified risk associated with the use of Ad26.COV2.S. Characterisation of this risk is provided in Section 16.4, Characterisation of Risks.

Methods

The Company global safety database was searched for medically confirmed and medically unconfirmed cases received during this reporting period and cumulatively which coded to the search criteria provided in Appendix 5.

Results/Discussion

Primary Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 38 (33 medically confirmed and 5 medically unconfirmed) initial, primary dose cases reporting TTS were identified. All 38 cases were serious and reported a total of 113 EOI (111 serious; 2 nonserious).

Of these 38 primary dose cases received during the interval reporting period, 4 were reported from Janssen Sponsored Clinical Studies and 34 from post-marketing sources (including spontaneous and solicited). No cases were reported from Janssen Supported Clinical Studies.

Cumulatively, 236 (192 medically confirmed and 44 medically unconfirmed) primary dose cases reporting TTS were identified. Of these cases, 235 were serious and 1 nonserious and reported a total of 1,023 EOI (1,009 serious; 14 nonserious).

Of the 236 cumulative primary dose cases received, 7 were reported from Janssen Sponsored Clinical Studies, 2 from Janssen Supported Clinical Studies, and 227 from post-marketing sources (including spontaneous and solicited cases).

Janssen Sponsored Clinical Studies Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 4 initial, primary dose cases were retrieved from Janssen Sponsored Clinical Studies. All 4 cases were reported from VAC31518COV3001. These 4 cases reported 8 EOI (6 serious; 2 nonserious). Of these 4 cases, the reported countries/territories of origin were the US (n=3), followed by Brazil (n=1). These cases concerned 3 males and 1 female. The age range was from 47 to 72 years.

The EOI included thrombocytopenia (n=3), deep vein thrombosis (n=2), and transient ischaemic attack, myocardial infarction, and platelet count decreased (n= 1 each). The mean and median TTO was 380.1 days and 369.5 days, respectively. The outcome of the 8 EOI was reported as resolved (n=6), resolving (n=1), and resolved with sequelae (n=1).

Janssen Supported Clinical Studies Primary Dose Cases

There were no primary dose cases retrieved from the search of the Company global safety database during the reporting period of 25 February 2022 to 24 August 2022.

Post-marketing Sources (Including Spontaneous and Solicited) Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 34 post-marketing sources (including spontaneous and solicited), initial, primary dose cases reporting TTS were identified. These 34 post-marketing, primary dose cases reported 105 serious EOI.

Cumulatively, 227 (183 medically confirmed and 44 medically unconfirmed) post-marketing, primary dose cases reporting TTS were identified. Of these cases, 226 were serious and 1 was nonserious and reported a total of 1,004 EOI (994 serious; 10 nonserious).

An overview of these cases is presented in Table 63 below.

Table 63: Characteristics of Post-marketing, Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Thrombosis With Thrombocytopenia Syndrome

Case Characteristics		Number of Cases Received During the Interval Reporting Period=34	Number of Cases Received Cumulatively=227
Sex	Female	11	117
	Male	15	94
	NR	8	16
Age (Years)[a]	18 to 35	4	38
Minimum: 20	36 to 50	12	78
Maximum: 70	51 to 64	9	65
Mean: 45.3	≥65	2	30
Median: 43	Adult	1	2
	NR	6	14
Sources	Spontaneous	25	217
	Clinical study (noninterventional; solicited)	9	10
Country/Territory[b]	Germany	14	29
	United States	8	134
	Italy	4	9
	Poland	3	7
	Belgium	1	2
	Brazil	1	5
	Ireland	1	1
	Portugal	1	2
	South Africa	1	2
Event Characteristics		**Number of Events=105**	**Number of Events=1,004**
Seriousness (Event Level)[c]	Serious	105	994
	Nonserious	0	10
Outcome (Event Level)[c]	Not resolved	17	362
	Resolved	14	76
	Fatal	12	136
	Resolving	4	96

Table 63: Characteristics of Post-marketing, Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Thrombosis With Thrombocytopenia Syndrome

	Resolved with sequelae	3	7
	NR	55	327

Key: NR=Not Reported

a: The calculation was based on the current reporting period (25 February 2022 to 24 August 2022). Age group was presented for cases where age was not reported.

b: Countries/Territories were presented in decreasing order for the current reporting period (25 February 2022 to 24 August 2022).

c: Seriousness and outcome have been presented for the events of interest. A single case may report more than 1 event of interest.

During the reporting period, of the 34 post-marketing, initial, primary dose cases, the most frequently reported countries/territories of origin (n≥4) were Germany (n=14), followed by the US (n=8) and Italy (n=4). These cases concerned 15 males, 11 females, and 8 did not report sex. The age range was from 20 to 70 years.

The frequency distribution of the MedDRA PTs of interest reported in post-marketing, primary dose cases is presented in Table 64 below. A single case may contain more than 1 EOI.

Table 64: Frequency of MedDRA PTs of Interest in Post-marketing, Primary Dose Cases Reporting Thrombosis with Thrombocytopenia Syndrome With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Thrombosis with thrombocytopenia syndrome	25	0	57	0
Cerebral venous sinus thrombosis	13	0	67	0
Pulmonary embolism	10	0	100	0
Deep vein thrombosis	9	0	59	0
Thrombocytopenia	6	0	129	0
Cerebrovascular accident	4	0	21	0
Platelet count decreased	3	0	99	7
Cerebral venous thrombosis	3	0	16	0
Embolism	2	0	4	0
Venous thrombosis	2	0	9	0
Portal vein thrombosis	2	0	20	0
Coronary artery thrombosis	2	0	4	0
Aortic thrombosis	2	0	10	0
Immune thrombocytopenia	2	0	19	0
Jugular vein thrombosis	2	0	17	0

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

a: The MedDRA PTs of interest with frequency ≥2 have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event of interest.

For the reporting period, the EOI (n≥3) included thrombosis with thrombocytopenia syndrome (n=25), cerebral venous sinus thrombosis (n=13), pulmonary embolism (n=10), deep vein thrombosis (n=9), thrombocytopenia (n=6), cerebrovascular accident (n=4), and platelet count decreased and cerebral venous thrombosis (n=3 each). The mean and median TTO were 36.4 days and 14 days respectively. Where reported (n=50), the outcomes were not resolved (n=17), resolved (n=14), fatal (n=12), resolving (n=4), and resolved with sequelae (n=3).

In addition, for the reporting period, the Company has stratified these 34 post-marketing, initial, primary dose cases by age group and sex and applied the TTS working case definitions from Brighton Collaboration (BC), CDC, and PRAC (see Table 65).

Table 65: Number of Cases by Age and Sex and Working Case Definitions for Post-marketing Cases Reporting Thrombosis With Thrombocytopenia With the Use of Ad26. COV2.S Vaccine for the Reporting Period (Cases=34; Events=105)

Age Group (Years)	18 to 35		36 to 50			51 to 64		≥65		NR	
Sex	**F**	**M**	**F**	**M**	**NR**	**F**	**M**	**F**	**M**	**F**	**NR**
CDC											
Tier 1	0	1	2	1	2	0	1	0	0	0	0
Tier 2	0	0	0	0	0	0	0	0	0	0	0
Neither	1	2	1	6	0	5	3	1	1	1	6
Total	**1**	**3**	**3**	**7**	**2**	**5**	**4**	**1**	**1**	**1**	**6**
Brighton Collaboration											
Level 1	0	1	2	2	0	2	2	0	0	1	0
Level 2	0	0	0	0	0	0	0	0	0	0	0
Level 3	0	0	0	0	2	0	0	0	0	0	0
Level 4	1	2	0	5	0	3	0	1	0	0	6
Level 5	0	0	1	0	0	0	2	0	1	0	0
Total	**1**	**3**	**3**	**7**	**2**	**5**	**4**	**1**	**1**	**1**	**6**
PRAC											
Confirmed	0	0	1	1	0	0	0	0	0	0	1
Probable	1	0	0	1	0	1	0	0	0	0	0
Possible	0	2	1	3	2	4	3	1	0	1	1
Unlikely	0	0	1	0	0	0	1	0	1	0	0
Criteria not met	0	1	0	2	0	0	0	0	0	0	4
Total	**1**	**3**	**3**	**7**	**2**	**5**	**4**	**1**	**1**	**1**	**6**

Key: CDC=Centers for Disease Control and Prevention; F=Female; M=Male; NR=Not Reported; PRAC=Pharmacovigilance Risk Assessment Committee

Fatal Post-marketing Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 8 post-marketing, initial, primary dose fatal cases with 12 fatal EOIs were retrieved. Of the 8 fatal cases, 3 concerned males, 2 females, and 3 did not report sex. The age range was 37 to 66 years. There were 4 patients in the age range of 36 to 50 years, 1 patient in the age ≥65 years, and the age was not reported in 3 cases. The mean and median TTO reported in these 12 fatal EOI were 72.5 days and 66 days, respectively. The fatal EOI were thrombosis with thrombocytopenia syndrome (n=4) and portal vein

thrombosis, brain stem stroke, cerebrovascular accident, thrombocytopenia, embolism, venous thrombosis, immune thrombocytopenia, and myocardial infarction (n=1 each).

Booster Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 4 (all medically confirmed) initial cases reported as booster were identified. All cases were serious and reported a total of 7 serious EOI. All 4 cases were heterologous and were reported from post-marketing sources (non-interventional solicited clinical study). No cases were reported from Janssen Sponsored Clinical Studies or Janssen Supported Clinical Studies.

Cumulatively, 5 (all medically confirmed) cases reported as booster were identified. All cases were serious and reported a total of 13 serious EOI. All 5 cases were heterologous. All 5 cumulative cases reported as booster were reported from post-marketing sources (including spontaneous and solicited cases). No cases were reported from Janssen Sponsored Clinical Studies or Janssen Supported Clinical Studies. Cumulatively, 1 medically confirmed, serious, heterologous, post-marketing case was identified reporting CVST and thrombocytopenia in a 48-year-old male who received a primary vaccination with an mRNA vaccine followed by a booster dose of Ad26.COV2.S 208 days later. The event of CVST occurred approximately 8 months after the primary mRNA vaccination and 12 days after the booster dose with Ad26.COV2.S. The patient had a history of hypertension and dyslipidaemia. The case was assessed as BC level 1, CDC Tier 1, and PRAC "possible". The outcome was fatal (unspecified). It was unknown whether autopsy was performed. No new information has been received since the last interval.

A cumulative booster dose CIOMS II LL is presented in Appendix 6.6.

Fatal Post-marketing Booster Dose Cases

There were no fatal cases reported as booster which were retrieved from the search of the Company global safety database during the interval reporting period of 25 February 2022 to 24 August 2022.

Literature ICSR

ICSR literature cases received during the reporting period of 25 February 2022 to 24 August 2022 were reviewed, and no information was identified that would change the characterisation of risk.

Conclusion

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

16.3.1.2. Guillain-Barré Syndrome

Introduction

According to the cRMP (version 4.0; dated 09 December 2021), GBS is an important identified risk associated with the use of Ad26.COV2.S. Characterisation of this risk is provided in Section 16.4, Characterisation of Risks.

Methods

The Company global safety database was searched for medically confirmed and medically unconfirmed cases received during this reporting period and cumulatively, which coded to the search criteria provided in Appendix 5.

Results/Discussion

Primary Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 72 (30 medically confirmed and 42 medically unconfirmed) initial, primary dose cases reporting GBS were identified. All these cases were serious and reported a total of 76 serious EOI.

Of these 72 primary dose cases received during the interval reporting period, 1 was reported from a Janssen Sponsored Clinical Study and 71 from post-marketing sources (including spontaneous and solicited). No cases were reported from Janssen Supported Clinical Studies.

Cumulatively, 593 (343 medically confirmed and 250 medically unconfirmed) primary dose cases reporting GBS were identified. Of these 593 cases, 592 were serious and 1 was nonserious and reported a total of 626 EOI (625 serious; 1 nonserious).

Of the 593 cumulative primary dose cases received, 9 were reported from Janssen Sponsored Clinical Studies, 2 from Janssen Supported Clinical Studies, and 582 from post-marketing sources (including spontaneous and solicited cases).

Janssen Sponsored Clinical Studies Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 1 initial, primary dose case reporting GBS was retrieved from a Janssen Sponsored Clinical Study. This serious case was from VAC31518COV3009 and concerned a 61-year-old female from [redacted]. This case reported a serious EOI of GBS with TTO of 466 days. The outcome for the EOI was reported as resolving.

Janssen Supported Clinical Studies Primary Dose Cases

There were no initial, primary dose cases retrieved from the search of the Company global safety database during the reporting period of 25 February 2022 to 24 August 2022.

Post-marketing Sources (Including Spontaneous and Solicited) Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 71 post-marketing sources (including spontaneous and solicited), initial, primary dose cases reporting GBS were retrieved. These 71 post-marketing, initial, primary dose cases reported 75 serious EOI.

Cumulatively, 582 (332 medically confirmed and 250 medically unconfirmed) post-marketing, primary dose cases reporting GBS were identified. All these cases were serious and reported a total of 615 serious EOI.

An overview of these cases is presented in Table 66 below.

Table 66: Characteristics of Post-marketing, Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting GBS

Case Characteristics		Number of Cases Received During the Interval Reporting Period=71	Number of Cases Received Cumulatively=582
Sex	Male	39	345
	Female	28	209
	NR	4	28
Age (Years)[a]	18 to 35	9	61
Minimum: 18	36 to 50	23	161
Maximum: 87	51 to 64	28	229
Mean: 50.1	≥65	5	79
Median: 51	Adult	1	5
	Elderly	0	2
	NR	5	45
Sources	Spontaneous	71	582
Country/Territory[b]	United States	24	315
	Germany	18	85
	South Africa	5	6
	Spain	5	24
	France	4	18
	Poland	4	5
	Brazil	2	12
	Greece	2	5
	Netherlands	2	17
	Austria	1	4
	Belgium	1	5
	Ireland	1	6
	Italy	1	20
	United Kingdom	1	1
Event Characteristics		**Number of Events=75**	**Number of Events=615**
Seriousness (Event Level)[c]	Serious	75	615
Outcome (Event Level)[c]	Not resolved	33	299
	Resolving	19	109

Table 66: Characteristics of Post-marketing, Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting GBS

Case Characteristics		Number of Cases Received During the Interval Reporting Period=71	Number of Cases Received Cumulatively=582
	Resolved with sequelae	5	23
	Resolved	2	32
	Fatal	1	4
	NR	15	148

Key: GBS=Guillain-Barré Syndrome; NR=Not Reported
a: The calculation was based on the current reporting period (25 February 2022 to 24 August 2022). Age group was presented for cases where age was not reported.
b: Countries/Territories were presented in decreasing order for the current reporting period (25 February 2022 to 24 August 2022).
c: Seriousness and outcome have been presented for the events of interest. A single case may report more than 1 event of interest.

Of these 71 post-marketing, initial, primary dose cases, the most frequently reported countries/territories of origin (n≥18) were the US (n=24) and Germany (n=18). These cases concerned 39 males, 28 females, and 4 did not report sex. The age range was from 18 to 87 years.

The frequency distribution of the MedDRA PTs of interest reported in post-marketing, primary dose cases is presented in Table 67 below. A single case may contain more than 1 EOI.

Table 67: Frequency of MedDRA PTs of Interest in Post-marketing, Primary Dose Cases Reporting GBS With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Guillain-Barre syndrome	62	0	529	0
Chronic inflammatory demyelinating polyradiculoneuropathy	8	0	37	0
Demyelinating polyneuropathy	2	0	17	0
Miller Fisher syndrome	2	0	19	0
Acute motor axonal neuropathy	1	0	2	0

Key: GBS=Guillain-Barré Syndrome; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: The MedDRA PTs of interest have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event of interest.

The most frequently reported EOI (n≥8) was GBS (n=62) and chronic inflammatory demyelinating polyradiculoneuropathy (n=8). The mean and median TTO were 52.8 and 15 days, respectively. Where reported (n=60), the outcome was not resolved (n=33), resolving (n=19), resolved with sequelae (n=5), resolved (n=2), and fatal (n=1).

Fatal Post-marketing Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 1 post-marketing, initial, primary dose case with 1 fatal EOI was retrieved. The fatal EOI was GBS. This fatal case concerned a 79-year-old female with concurrent conditions of hypertensive cardiomyopathy and GBS who experienced an exacerbation of GBS approximately 276 days following vaccination with Ad26.COV2.S. It was unknown if an autopsy was reported.

Booster Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 8 (no medically confirmed and 8 medically unconfirmed) initial cases reported as booster were identified. All cases were serious and reported a total of 8 serious EOI. Of these cases, 5 were heterologous and 3 were homologous.

All 8 booster cases reported as booster during the interval were reported from post-marketing sources (including spontaneous and solicited). No cases were reported from Janssen Sponsored Clinical Studies or Janssen Supported Clinical Studies.

Cumulatively, 10 (1 medically confirmed and 9 medically unconfirmed) cases reported as booster were identified. All cases were serious and reported a total of 10 serious EOI. Of these cases, 7 were heterologous and 3 were homologous.

All 10 cumulative cases reported as booster were reported from post-marketing sources (including spontaneous and solicited cases). No cases were reported from Janssen Sponsored Clinical Studies or Janssen Supported Clinical Studies.

A cumulative booster dose CIOMS II LL is presented in Appendix 6.7.

Janssen Sponsored and Janssen Supported Clinical Studies (Booster Dose Cases)

There were no initial cases reported as booster which were retrieved from the search of the Company global safety database during the interval reporting period of 25 February 2022 to 24 August 2022 for either the Janssen Sponsored or Janssen Supported Clinical trials.

Post-marketing Sources (Including Spontaneous and Solicited) Booster Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 8 post-marketing sources (including spontaneous and solicited),initial cases reported as booster were retrieved. These 8 post-marketing, booster dose cases reported 8 serious EOI.

Cumulatively, 10 (1 medically confirmed and 9 medically unconfirmed) post-marketing cases reported as booster were identified. All cases were serious and reported a total of 10 serious EOI.

An overview of these post-marketing, booster dose cases is presented in Table 68 below.

Table 68: Characteristics of Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting GBS

Case Characteristics		Number of Cases Received During the Interval Reporting Period=8	Number of Cases Received Cumulatively=10
Sex	Male	6	6
	Female	2	3
	NR	0	1
Age (Years)[a]	18 to 35	1	1
Minimum: 24	36 to 50	1	2
Maximum: 76	51 to 64	4	4
Mean: 54.9	≥65	2	2
Median: 57.5	NR	0	1
Country/Territory[b]	Brazil	2	3
	Germany	2	2
	Netherlands	1	1
	Philippines	1	1
	South Africa	1	1
	United States	1	2
Sources	Spontaneous	8	10
Classification	Heterologous	5	7
	Homologous	3	3
Event Characteristics		**Number of Events=8**	**Number of Events=10**
Seriousness (Event Level)[c]	Serious	8	10
Outcome (Event Level)[c]	Not resolved	3	3
	Fatal	1	1
	Resolved	1	1
	Resolving	1	1
	NR	2	4

Key: GBS=Guillain-Barré Syndrome; NR=Not Reported

a: The calculation was based on the current reporting period (25 February 2022 to 24 August 2022).

b: Countries/Territories were presented in decreasing order for the current reporting period (25 February 2022 to 24 August 2022).

c: Seriousness and outcome have been presented for the events of interest.

Of these 8 post-marketing, initial cases reported as booster, the most frequently reported countries/territories of origin (n≥2) were Brazil and Germany (n=2 each). These cases concerned 6 males and 2 females. The age range was from 24 to 76 years.

The frequency distribution of the MedDRA PTs of interest reported in post-marketing cases reported as booster is presented in Table 69 below.

Table 69: Frequency of MedDRA PTs of Interest in Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting GBS

MedDRA PTs	Number of Events Reported During the Interval Reporting Period		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Guillain-Barre syndrome	8	0	10	0

Key: GBS=Guillain-Barré Syndrome; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term

The EOI reported was Guillain-Barré Syndrome (n=8). The mean and median TTO were 132.8 and 100 days, respectively. Where reported (n=6), the outcome was not resolved (n=3), fatal (n=1), resolved (n=1), and resolving (n=1).

Fatal Post-marketing Booster Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 1 initial, case reported as booster with 1 fatal EOI was retrieved. This case from South Africa concerned a 37-year-old male who experienced GBS, slurred speech, inability to walk, and tingling in feet/hands approximately 2 days following a booster dose of Ad26.COV2.S. An unspecified duration later, following booster vaccination, the patient died from GBS. It was unspecified whether an autopsy was performed. No additional details were provided including relevant medical history/concurrent conditions, clinical course/treatment, and supporting diagnostic data.

Literature ICSR

ICSR literature cases received during the reporting period of 25 February 2022 to 24 August 2022 were reviewed, and there was no new or significant information identified which changed the characterisation of this risk.

Conclusion

Based on the evaluation of the cases, and review of safety from other sources, the information is consistent with the information known about GBS. The Company will continue to closely monitor GBS as an important identified risk

16.3.1.3. Venous Thromboembolism

Introduction

Venous thromboembolism has been reclassified as an important identified risk in the EU RMP. The cRMP is in the process of being updated to reflect the reclassification.

According to the cRMP (version 4.0; dated 09 December 2021), VTE is an important potential risk associated with the use of Ad26.COV2.S. However, on 10 May 2022, based on the evidence from post-marketing data sources, the Company upgraded VTE from an important potential to an important identified risk. The cRMP is in the process of being updated to reflect this change. Characterisation of this risk is provided in Section 16.4, Characterisation of Risks.

Methods

The Company global safety database was searched for medically confirmed and medically unconfirmed cases received during this reporting period and cumulatively, which were coded to the search criteria provided in Appendix 5.

Results/Discussion

Primary Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 559 (317 medically confirmed and 242 medically unconfirmed), initial, primary dose cases reporting VTE were identified. Of these 559 cases, 522 were serious and 37 were nonserious and reported a total of 740 EOI (686 serious, 54 nonserious).

Of these 559 primary dose cases received during the interval reporting period, 63 were reported from Janssen Sponsored Clinical Studies, 1 from a Janssen Supported Clinical Study, and 495 from post-marketing sources (including spontaneous and solicited).

Cumulatively, 4,693 (2,862 medically confirmed and 1,831 medically unconfirmed) primary dose cases reporting VTE were identified. Of these cases, 4,539 cases were serious and 154 were nonserious and reported a total of 6,460 EOI (6,201 serious; 259 nonserious).

Of the 4,693 cumulative primary dose cases received, 218 were reported from Janssen Sponsored Clinical Studies, 44 from Janssen Supported Clinical Studies, and 4,431 from post-marketing sources (including spontaneous and solicited cases).

Janssen Sponsored Clinical Studies Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 63 initial, primary dose cases reporting VTE were retrieved from Janssen Sponsored Clinical Studies. Of the 63 cases, 37 were from VAC31518COV3001, 23 from VAC31518COV3009, 2 from VAC31518COV1001, and 1 from VAC31518COV3005. These 63 cases reported 69 EOI (49 serious, 20 nonserious). Of these 63 cases, the most frequently reported countries/territories of origin (n≥9) were the US (n=25), followed by Brazil (n=10) and South Africa (n=9). These cases concerned 37 males and 26 females. The age range was from 27 to 84 years.

Upon case level review, it has been determined that 6 patients were administered placebo. These cases [redacted] and [redacted]) are in the process of being updated and the change will be reflected in the next scheduled PBRER.

The most frequently reported EOI (n≥4) included deep vein thrombosis (n=22), pulmonary embolism (n=17), cerebrovascular accident (n=9), and cerebral infarction and venous thrombosis limb (n=4 each). The mean and median TTO were 393.8 and 388.5 days, respectively. Where reported (n=67), the outcomes were resolved (n=28), resolving (n=25), not resolved (n=8), resolved with sequelae (n=5), and fatal (n=1).

Janssen Supported Clinical Studies Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 1 initial, primary dose case reporting VTE was retrieved from a Janssen Supported Clinical Study. The case was from VAC31518COV3021 and concerned an 84-year-old male from South Africa reporting a serious EOI of cerebellar infarction. The TTO was 6 days. The outcome for the EOI was reported as resolving.

Post-marketing Sources (Including Spontaneous and Solicited) Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 495 post-marketing sources (including spontaneous and solicited), initial, primary dose cases reporting VTE were retrieved. These 495 post-marketing, initial, primary dose cases reported 670 EOI (636 serious; 34 nonserious).

Cumulatively, 4,431 (2,600 medically confirmed and 1,831 medically unconfirmed) post-marketing, primary dose cases reporting VTE were identified. Of these cases, 4,328 were serious and 103 were nonserious and reported a total of 6,171 EOI (5,979 serious; 192 nonserious).

An overview of these cases is presented in Table 70 below.

Table 70: Characteristics of Post-marketing, Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting VTE

Case Characteristics		Number of Cases Received During the Interval Reporting Period=495	Number of Cases Received Cumulatively=4,431
Sex	Male	225	1,989
	Female	209	2,224
	NR	61	218
Age (Years)[a]	<18	2	6
Minimum: 0.25	18 to 35	65	545
Maximum: 95	36 to 50	124	1,106
Mean: 52.2	51 to 64	146	1,355
Median: 53	≥65	91	984
	Adult	7	33
	Elderly	1	8
	Neonate	0	1
	NR	59	393
Sources	Spontaneous	474	4,393
	Clinical study (noninterventional; solicited)	21	38
Country/Territory[b]	United States	242	3,240
	Germany	72	362
	Poland	40	70
	South Africa	31	43
	Philippines	24	46
	Greece	12	37

Table 70: Characteristics of Post-marketing, Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting VTE

Case Characteristics		Number of Cases Received During the Interval Reporting Period=495	Number of Cases Received Cumulatively=4,431
	Brazil	11	36
	Italy	11	88
	Netherlands	10	109
	France	7	101
	Austria	6	31
	Latvia	5	14
Event Characteristics		**Number of Events=670**	**Number of Events=6,171**
Seriousness (Event Level)[c]	Serious	636	5,979
	Nonserious	34	192
Outcome (Event Level)[c]	Not resolved	217	2,638
	Resolved	89	766
	Resolving	67	516
	Fatal	41	409
	Resolved with sequelae	21	75
	NR	235	1,767

Key: NR=Not Reported; VTE=Venous Thromboembolism
a: The calculation was based on the current reporting period (25 February 2022 to 24 August 2022). Age group was presented for cases where age was not reported.
b: Countries/Territories with frequency ≥5 were presented in decreasing order for the current reporting period (25 February 2022 to 24 August 2022).
c: Seriousness and outcome have been presented for the events of interest. A single case may report more than 1 event of interest.

Of these 495 post-marketing, initial, primary dose cases, the most frequently reported countries/territories of origin (n≥40) were the US (n=242), followed by Germany (n=72) and Poland (n=40). These cases concerned 225 males, 209 females, and 61 did not report sex. The age range was from 0.25 to 95 years.

The frequency distribution of the MedDRA PTs of interest reported in post-marketing, primary dose cases is presented in Table 71 below. A single case may contain more than 1 EOI.

Table 71: Frequency of MedDRA PTs of Interest in Post-marketing, Primary Dose Cases Reporting VTE With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Thrombosis	133	0	1,314	0
Pulmonary embolism	79	0	938	1
Deep vein thrombosis	65	0	782	1
Cerebrovascular accident	62	0	619	0

Table 71: Frequency of MedDRA PTs of Interest in Post-marketing, Primary Dose Cases Reporting VTE With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Thrombosis with thrombocytopenia syndrome	28	0	73	0
Cerebral venous sinus thrombosis	24	0	142	0
Hemiparesis	23	0	177	0
Ultrasound Doppler abnormal	14	6	209	49

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term; VTE=Venous Thromboembolism

a: The MedDRA PTs of interest with a frequency ≥20 have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event of interest.

The most frequent EOI (n≥20) included thrombosis (n=133), pulmonary embolism (n=79), deep vein thrombosis (n=65), cerebrovascular accident (n=62), thrombosis with thrombocytopenia syndrome (n=28), cerebral venous sinus thrombosis (n=24), hemiparesis (n=23), and ultrasound Doppler abnormal (n=20). The mean and median TTO were 90.6 and 37.0 days, respectively. Where reported (n=435), the outcomes were not resolved (n=217), resolved (n=89), resolving (n=67), fatal (n=41), and resolved with sequelae (n=21).

Fatal Post-marketing Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 44 post-marketing, initial, primary dose fatal cases were retrieved. Of these 44 cases, 32 reported fatal EOI (n=41). The fatal EOI were pulmonary embolism and thrombosis (n=8 each), cerebrovascular accident (n=6), central venous catheterisation and thrombosis with thrombocytopenia syndrome (n=4 each), cerebral thrombosis and hemiparesis (n=2 each), and brain stem stroke, cerebrovascular disorder, deep vein thrombosis, embolism, portal vein thrombosis, superficial vein thrombosis, and venous thrombosis (n=1 each). The mean and median TTO for the fatal EOIs (where onset dates were available) were 130.2 days and 117 days, respectively. Of the 32 cases reporting fatal EOI (see Appendix 6.8.1), 20 concerned males, 8 females, and 4 had no sex reported. The age range was 35 to 95 years, with mean and median of 62.8 and 64.5 years, respectively. Among patients where age was reported (28/32), 1 was in the age range of 18 to 35 years, 5 were in the age range of 36 to 50 years, 8 were in the age range of 51 to 64 years, and 14 were ≥65 years. Six of the 32 cases co-reported thrombocytopenia.

Booster Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 69 (34 medically confirmed and 35 medically unconfirmed) initial cases reported as booster were identified. There

were 64 serious and 5 nonserious cases and reported a total of 93 EOI (85 serious; 8 nonserious). Of these cases, 34 were heterologous and 35 were homologous.

Of these 69 cases reported as booster during the interval, 6 were reported from Janssen Sponsored Clinical Studies and 63 from post-marketing sources (including spontaneous and solicited). No cases were reported from Janssen Supported Clinical Studies.

Cumulatively, 135 (68 medically confirmed and 67 medically unconfirmed) cases reported as booster were identified. Of these cases, 129 cases were serious and 6 were nonserious and reported a total of 177 EOI (168 serious; 9 nonserious). Of these cases, 46 were heterologous and 89 were homologous.

Of the 135 cumulative cases reported as booster, 9 were reported from Janssen Sponsored Clinical Studies and 126 from post-marketing sources (including spontaneous and solicited cases). No cases were reported from Janssen Supported Clinical Studies.

A cumulative booster dose CIOMS II LL is presented in Appendix 6.8.2.

Janssen Sponsored Clinical Studies Booster Dose Cases

During the interval reporting period of 25 February 2022 to 24 August 2022, 6 initial cases reported as booster were retrieved from Janssen Sponsored Clinical Studies. All 6 cases were from VAC31518COV3001 and VAC31518COV3009 (n=3 each). These 6 cases reported 6 EOI (2 serious; 4 nonserious). Of these 6 cases, the most frequently reported country/territory of origin (n≥2) was the US (n=2). These cases concerned 4 females and 2 males. The age range was from 45 to 65 years.

The EOI included deep vein thrombosis and pulmonary embolism (n=2 each), and cerebrovascular accident and venous thrombosis limb (n=1 each). The mean and median TTO were 282.8 and 231.5 days, respectively. The outcome for all EOI was either not resolved or resolving (n=3 each).

Janssen Supported Clinical Studies Booster Dose Cases

There were no initial cases reported as booster which were retrieved from the search of the Company global safety database during the interval reporting period of 25 February 2022 to 24 August 2022.

Post-marketing Sources (Including Spontaneous and Solicited) Booster Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 63 post-marketing sources (including spontaneous and solicited), initial cases reported as booster were retrieved. These 63 post-marketing booster dose cases reported 87 EOI (83 serious; 4 nonserious).

Cumulatively, 126 (59 medically confirmed and 67 medically unconfirmed) post-marketing, cases reported as booster were identified. Of these cases, 125 cases were serious and 1 was nonserious and reported a total of 168 EOI (164 serious; 4 nonserious).

An overview of these post-marketing, booster dose cases is presented in Table 72 below.

Table 72: Characteristics of Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting VTE

Case Characteristics		Number of Cases Received During the Interval Reporting Period=63	Number of Cases Received Cumulatively=126
Sex	Male	36	67
	Female	27	55
	NR	0	4
Age (Years)[a]	<18	1	1
Minimum: 17	18 to 35	11	14
Maximum: 93	36 to 50	20	33
Mean: 51.3	51 to 64	15	30
Median: 48	≥65	14	31
	Adult	0	2
	NR	2	15
Country/Territory[b]	United States	28	84
	Germany	14	16
	Brazil	11	14
	South Africa	3	3
	Austria	2	2
Sources	Spontaneous	59	121
	Clinical study (noninterventional; solicited)	4	5
Classification	Heterologous	34	46
	Homologous	29	80
Event Characteristics		**Number of Events=87**	**Number of Events=168**
Seriousness (Event Level)[c]	Serious	83	164
	Nonserious	4	4
Outcome (Event Level)[c]	Not resolved	33	52
	Resolved	16	30
	Resolving	7	18
	Resolved with sequelae	6	7
	Fatal	2	8
	NR	23	53

Key: NR=Not Reported; VTE=Venous Thromboembolism

a: The calculation was based on the current reporting period (25 February 2022 to 24 August 2022). Age group was presented for cases where age was not reported.

b: Countries/Territories with frequency ≥2 were presented in decreasing order for the current reporting period (25 February 2022 to 24 August 2022).

c: Seriousness and outcome have been presented for the events of interest. A single case may report more than 1 event of interest.

Of these 63 post-marketing, initial cases reported as booster, the most frequently reported countries/territories of origin (n≥11) were the US (n=28), followed by Germany (n=14) and Brazil (n=11). These cases concerned 36 males and 27 females. The age range was from 17 to 93 years.

The frequency distribution of the MedDRA PTs of interest reported in post-marketing cases reported as booster is presented in Table 73 below. A single case may contain more than 1 EOI.

Table 73: Frequency of MedDRA PTs of Interest in Post-Marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting VTE

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Thrombosis	16	0	37	0
Deep vein thrombosis	15	0	26	0
Pulmonary embolism	11	0	20	0
Ultrasound Doppler abnormal	5	1	8	1
Thrombosis with thrombocytopenia syndrome	4	0	4	0
Cerebral infarction	3	0	6	0
Cerebral thrombosis	2	0	3	0
Cerebral venous sinus thrombosis	2	0	3	0
Cerebrovascular accident	2	0	16	0
Hemiparesis	2	0	3	0
Monoplegia	2	0	2	0
Pulmonary thrombosis	2	0	8	0
Thrombectomy	2	0	2	0

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term; VTE=Venous Thromboembolism

a: The MedDRA PTs of interest with a frequency ≥2 have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event of interest.

The most frequent EOI (n≥10) included thrombosis (n=16), deep vein thrombosis (n=15), and pulmonary embolism (n=11). The mean and median TTO were 109.2 and 80.0 days, respectively. Where reported (n=64), the outcomes were not resolved (n=33), resolved (n=16), resolving (n=7), resolved with sequelae (n=6), and fatal (n=2).

Fatal Post-marketing Booster Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 3 initial, fatal cases reported as booster were retrieved. Of these 3 cases, 2 reported a fatal EOI (n=2). The fatal EOI was thrombosis (n=2). In both cases, the EOI occurred after the mRNA booster vaccine was administered at 9 days after the booster dose in 1 case while in the other case latency was unspecified.

Literature ICSR

There was a total of 39 ICSR literature cases (35 cases involving primary dose administration [including 13 cases with multiple unidentifiable patients] and 4 cases reported as the booster dose) received during the reporting period of 25 February 2022 to 24 August 2022. Of

the 39 literature cases, 25 cases reported TTS. No information was identified that would change the characterisation of risk.

Recategorisation of the Risk

In May 2022, based on sufficient converging evidence observed in the post-marketing setting, the Company made a decision to upgrade VTE from an important potential risk to an important identified risk. VTE was added as an adverse reaction to the CCDS based on the following:

- The presence of cases in close temporal association with no clear confounders in the Company global safety database.
- The O/E ratio was statistically significant above 1 (LB of 95% CI: >1) for Deep vein thrombosis and Pulmonary embolism in the restricted sensitivity analysis (18 to 59 years of age group).
- RWE rapid cycle analysis showed that the risk of VTE after the first Ad26.COV2.S dose in the 1 to 28 day risk window (the specified time window of concern for VTE) was increased ~1.25 times.
- Literature search identified an increase in frequency/RR/OR in individuals vaccinated with chimpanzee adenovector-based COVID-19 vaccines (other than Ad26.COV2.S) compared to mRNA/background rates.

Conclusion

Based on the evaluation of the cases, and review of safety from other sources, the information is consistent with the information known about VTE. Since the Company changed the risk from potential to important in May 2022, the Company will continue to closely monitor VTE as an important identified risk.

16.3.2. New Information on Important Potential Risks

16.3.2.1. Vaccine-Associated Enhanced Disease, Including Vaccine-Associated Enhanced Respiratory Disease

Introduction

According to the cRMP (version 4.0; dated 09 December 2021), vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD), is an important potential risk associated with the use of Ad26.COV2.S. Characterisation of this risk is provided in Section 16.4, Characterisation of Risks.

Methods

The Company global safety database was searched for medically confirmed and medically unconfirmed cases received during this reporting period and cumulatively, which coded to the search criteria provided in Appendix 5.

Results/Discussion

Primary Dose

There were no initial, primary dose cases retrieved from the search of the Company global safety database during the reporting period of 25 February 2022 to 24 August 2022.

Cumulatively, 1 medically confirmed, serious, primary dose case reporting VAED, including VAERD, was identified. This case reported a total of 1 serious EOI of VAED from a post-marketing spontaneous source. The outcome was not reported for this EOI.

Booster Dose

There were no initial cases reported as booster, which were retrieved from the search of the Company global safety database during the interval reporting period of 25 February 2022 to 24 August 2022. In addition, cumulatively, there were no cases reported as booster.

Literature ICSR

No ICSR literature cases were received during the reporting period of 25 February 2022 to 24 August 2022.

Conclusion

Based on the review of the literature (ie, Section 11), ongoing/completed clinical studies (ie, Sections 7, 8, and 9), and single case retrieved cumulatively from the Company global safety database, no new significant safety information was identified for the important potential risk of VAED, including VAERD.

16.3.2.2. Immune Thrombocytopenia

Introduction

According to the cRMP (version 4.0; dated 09 December 2021), ITP is an important potential risk associated with the use of Ad26.COV2.S. In the EU RMP (version 2.5, dated 13 January 2022), this risk is characterised as "Thrombocytopenia, including ITP" and is listed as an important identified risk. Characterisation of this risk is provided in Section 16.4, Characterisation of Risks.

Methods

The Company global safety database was searched for medically confirmed and medically unconfirmed cases received during this reporting period and cumulatively which coded to the search criteria provided in Appendix 5.

The case definition for this topic is described within: as all cases that were retrieved from the database were individually reviewed and all cases meeting criteria for aggregate presentation were those that reported an EOI within the risk window of 42 days (or those where risk window was not reported), an identifiable patient with evidence of thrombocytopenia. All cases were reviewed for evidence of thrombocytopenia per the interim BC case definition v 10.16.3 for thrombocytopenia (Brighton Collaboration 2021a); there is no BC criteria for immune

thrombocytopenia. Cases are further assessed using a case definition modified from the American Society of Hematology (ASH) (Kelton 2018). It is acknowledged that the threshold appears very high for a case to be able to fulfil the definition of 'confirmed' (Table 74).

Table 74: Summary of ASH Case Definition for Immune Thrombocytopenia

	Platelet	Treatment	Anti-platelet Autoantibody Test	Causes of Thrombocytopenia (Clinical Manifestations)
Confirmed	A platelet count <100x10^9/L, with the exclusion of other causes of thrombocytopenia AND a low platelet count nadir (<20x10^9/L)	AND a platelet count response to therapy (corticosteroids, IVIG, or treatment of the underlying secondary cause)	AND a positive anti-platelet autoantibody test	(exclusion of other causes of thrombocytopenia)
Likely	A platelet count <100x10^9/L; OR a low platelet count nadir (<20x10^9/L)	OR a platelet count response to therapy (corticosteroids, IVIG, or treatment of the underlying secondary cause)	OR a positive anti-platelet autoantibody test	AND with the exclusion of other causes of thrombocytopenia
Suspect	-	-	-	Reported thrombocytopenia without a reported underlying or associated cause
Excluded	-	-	-	No thrombocytopenia secondary to other disease (eg, tumour)

Key: ASH=American Society of Hematology; IVIG=Intravenous Immunoglobulin

Results/Discussion

Primary Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 302 initial, primary dose cases reporting ITP were retrieved. Out of 302 cases, 30 (14 medically confirmed and 16 medically unconfirmed) cases were identified from post-marketing sources (including spontaneous and solicited) to meet the ASH case definition for ITP.

Cumulatively, 417 (304 medically confirmed and 113 medically unconfirmed) primary dose cases reporting ITP per ASH case definitions are presented. Of these cases, 305 were serious and 112 were nonserious and reported a total of 478 EOI (355 serious; 123 nonserious).

Of the 417 cumulative primary dose cases, 14 were reported from Janssen Sponsored Clinical Studies, 3 from Janssen Supported Clinical Studies, and 400 from post-marketing sources (including spontaneous and solicited cases).

Janssen Sponsored and Janssen Supported Clinical Studies Cases

A detailed analysis of events of thrombocytopenia identified from sponsored clinical trials is available in Appendix 6.9.1.

Post-marketing Sources (Including Spontaneous and Solicited) Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 30 post-marketing sources (including spontaneous and solicited), initial, primary dose cases reporting ITP per ASH case definitions are presented. Of these 30 cases, 27 were serious and 3 were nonserious and reported a total of 37 EOI (32 serious; 5 nonserious).

Cumulatively, 400 (287 medically confirmed and 113 medically unconfirmed) post-marketing, primary dose cases reporting ITP per ASH case definitions are presented. Of these cases, 297 cases were serious and 103 were nonserious and reported a total of 461 EOI (347 serious, 114 nonserious).

An overview of these cases is presented in Table 75 below.

Table 75: Characteristics of Post-marketing, Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Immune Thrombocytopenia

Case Characteristics		Number of Cases Received During the Interval Reporting Period=30	Number of Cases Received Cumulatively=400
Sex	Female	20	191
	Male	10	207
	NR	0	2
Age (Years)[a]	18 to 35	7	55
Minimum: 22	36 to 50	7	150
Maximum: 97	51 to 64	7	116
Mean: 51.1	≥65	6	67
Median: 50	Adult	1	4
	NR	2	8
Sources	Spontaneous	29	396
	Clinical study (noninterventional; solicited)	1	4
Country/Territory[b]	United States	14	188
	Germany	5	38
	France	3	15
	Austria	2	7
	South Africa	2	3
	Cote d'Ivoire	1	1
	Colombia	1	2
	Latvia	1	2
	Greece	1	1

Table 75: Characteristics of Post-marketing, Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Immune Thrombocytopenia

Case Characteristics		Number of Cases Received During the Interval Reporting Period=30	Number of Cases Received Cumulatively=400
Event Characteristics		**Number of Events=37**	**Number of Events=461**
Seriousness (Event Level)[c]	Serious	32	347
	Nonserious	5	114
Outcome (Event Level)[c]	Not resolved	13	142
	Resolved	7	83
	Resolving	4	45
	Fatal	2	17
	Resolved with sequelae	1	5
	NR	10	169

Key: NR=Not Reported
a: The calculation was based on the current reporting period (25 February 2022 to 24 August 2022). Age group was presented for cases where age was not reported.
b: Countries/Territories were presented in decreasing order for the current reporting period (25 February 2022 to 24 August 2022).
c: Seriousness and outcome have been presented for the events of interest. A single case may report more than 1 event of interest.

Out of the 30 post-marketing, initial, primary dose cases, 11 reported TTO beyond 42 days from the day of vaccination and hence were considered outside the risk window and TTO was not reported in 5 cases. The mean and median TTO were 72.5 days and 35 days, respectively. The most frequently reported countries/territories of origin (n≥5) were the US (n=14), followed by Germany (n=5). These cases concerned 10 males in the age range from 28 to 83 years and 20 females in the age range from 22 to 97 years.

The frequency distribution of the MedDRA PTs of interest reported in post-marketing, primary dose cases is presented in Table 76 below. A single case may contain more than 1 EOI.

Table 76: Frequency of MedDRA PTs of Interest in Post-marketing, Primary Dose Cases Reporting Immune Thrombocytopenia With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	**Nonserious**	**Serious**	**Nonserious**
Platelet count decreased	12	5	113	36
Thrombocytopenia	10	0	136	0
Immune thrombocytopenia	9	0	77	0
Thrombosis with thrombocytopenia syndrome	1	0	4	0

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: The MedDRA PTs of interest have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event of interest.

The EOI included platelet count decreased (n=17), thrombocytopenia (n=10), immune thrombocytopenia (n=9), and thrombosis with thrombocytopenia syndrome (n=1). Where reported (n=27), the outcomes were not resolved (n=13), resolved (n=7), resolving (n=4), fatal (n=2), and resolved with sequelae (n=1).

Fatal Post-marketing Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, there was 1 post-marketing, primary dose, fatal case with 2 fatal EOIs that met the ASH case definition for ITP with TTO beyond 42 days. This fatal case concerned a 73-year-old male with EOIs of thrombocytopenia and platelet count decreased, which was reported 271 days post-vaccination.

Booster Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 60 initial, booster dose cases reporting ITP were retrieved. Out of 60 cases, 8 (1 medically confirmed and 7 medically unconfirmed) initial cases reported as booster were identified to meet the ASH case definition for ITP. There were 7 serious cases and 1 nonserious and reported a total of 8 EOI (3 serious, 5 nonserious). Of these cases, 6 were heterologous and 2 were homologous.

All 8 booster cases received during the interval reporting period were reported from post-marketing sources (including spontaneous and solicited). None of the cases were reported from Janssen Sponsored Clinical Studies or Janssen Supported Clinical Studies.

Cumulatively, 15 (6 medically confirmed and 9 medically unconfirmed) cases reported as booster were identified to meet the ASH case definition for ITP. Of these cases, 12 were serious and 3 were nonserious and reported a total of 16 EOI (8 serious, 8 nonserious). Of these cases, 8 were heterologous and 7 were homologous.

All 15 booster cases received cumulatively were reported from post-marketing sources (including spontaneous and solicited). None of the cases were reported from Janssen Sponsored Clinical Studies or Janssen Supported Clinical Studies.

A cumulative booster dose CIOMS II LL is presented in Appendix 6.9.2.

Janssen Sponsored and Janssen Supported Clinical Studies (Booster Dose Cases)

There were no initial cases reported as booster which were retrieved from the search of the Company global safety database during the interval reporting period of 25 February 2022 to 24 August 2022 for either the Janssen Sponsored or Janssen Supported Clinical Studies.

Post-marketing Sources (Including Spontaneous and Solicited) Booster Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 8 post-marketing sources (including spontaneous and solicited), initial cases reported as booster were retrieved. These 8 post-marketing booster dose cases reported 8 EOI (3 serious; 5 nonserious).

Cumulatively, 15 (6 medically confirmed and 9 medically unconfirmed) post-marketing cases reported as booster were identified. Of these cases, 12 were serious and 3 were nonserious and reported a total of 16 EOI (8 serious; 8 nonserious).

An overview of these cases is presented in Table 77 below.

Table 77: Characteristics of Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Immune Thrombocytopenia

Case Characteristics		Number of Cases Received During the Interval Reporting Period=8	Number of Cases Received Cumulatively=15
Sex	Female	4	7
	Male	4	8
Age (Years)[a]	18 to 35	1	1
Minimum: 33	36 to 50	0	2
Maximum: 81	51 to 64	5	7
Mean: 59.6	≥65	2	4
Median: 58	NR	0	1
Country/Territory[b]	United States	4	9
	Germany	2	3
	Brazil	1	1
	South Africa	1	1
	Greece	0	1
Sources	Spontaneous	6	13
	Clinical study (noninterventional; solicited)	2	2
Classification	Heterologous	6	8
	Homologous	2	7
Event Characteristics		**Number of Events=8**	**Number of Events=16**
Seriousness (Event Level)[c]	Serious	3	8
	Nonserious	5	8
Outcome (Event Level)[c]	Not resolved	4	9
	Resolved	1	1
	Fatal	0	2
	NR	3	4

Key: NR=Not Reported

a: The calculation was based on the current reporting period (25 February 2022 to 24 August 2022).

b: Countries/Territories were presented in decreasing order for the current reporting period (25 February 2022 to 24 August 2022).

c: Seriousness and outcome have been presented for the events of interest.

Of these 8 post-marketing initial cases reported as booster, the most frequently reported countries/territories of origin (n≥2) were US (n=4) followed by Germany (n=2). These cases concerned 4 males in the age range from 55 to 75 years and 4 females in the age range from 33 to 81 years.

The frequency distribution of the MedDRA PTs of interest reported in post-marketing cases reported as booster is presented in Table 78 below.

Table 78: Frequency of MedDRA PTs of Interest in Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Immune Thrombocytopenia

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Platelet count decreased	2	5	3	8
HELLP syndrome	1	0	1	0

Key: HELLP=Haemolysis, Elevated liver enzymes, Low platelet count; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term

a: The MedDRA PTs of interest have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022).

The EOIs included platelet count decreased (n=7) and HELLP syndrome (n=1). The mean and median TTO were 61.6 days and 38 days, respectively. Where reported (n=5), the outcomes were not resolved (n=4) and resolved (n=1).

Fatal Post-marketing Booster Dose Cases

There were no fatal cases reported as booster which were retrieved from the search of the Company global safety database during the interval reporting period of 25 February 2022 to 24 August 2022.

Literature ICSR

ICSR literature cases received during the reporting period of 25 February 2022 to 24 August 2022 were reviewed, and no information was identified that would change the characterisation of risk.

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 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.

16.3.3. 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.

16.3.4. 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.

16.3.5. Update on Missing Information

16.3.5.1. Use During Pregnancy

Introduction

According to the cRMP (version 4.0; dated 09 December 2021), use during pregnancy is a missing information associated with the use of Ad26.COV2.S. Characterisation of this risk is provided in Section 16.4, Characterisation of Risks. This section will contain information on cases reporting use during pregnancy and use in breastfeeding women.

Methods

The Company global safety database was searched for medically confirmed and medically unconfirmed cases received during this reporting period and cumulatively, which coded to the search criteria provided in Appendix 5. This section will include combined counts of primary and booster dose cases.

Results/Discussion

Primary Dose and Booster Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 479 (264 medically confirmed and 215 medically unconfirmed) primary dose and 91 (34 medically confirmed and 57 medically unconfirmed) booster dose cases were retrieved by the search strategy for use in pregnancy/use in breastfeeding women.

Of these 570 interval cases, 37 did not meet the criteria for inclusion in this section (cases of congenital anomalies reported in patients and not related to pregnancy or lactation exposure). In 2 cases, placebo was given and Ad26.COV2.S was not involved. Additionally, 73 cases reported maternal exposure to vaccine >3 months before pregnancy and 15 reported paternal exposure to vaccine >2 weeks before pregnancy. Three cases concerned multiple patients without individual patient identifiers and 3 were duplicate cases. These 133 cases are not discussed further.

Of the remaining 437 cases received during the interval reporting period, 66 were reported from Janssen Sponsored Clinical Studies, 8 from Janssen Supported Clinical Studies, and 363 from post-marketing sources (including spontaneous and solicited sources). During this period, 421 cases (167 serious; 254 nonserious) reporting exposure during pregnancy (including 2 linked cases reporting lactation exposure along with pregnancy exposure in the same baby and 1 reporting lactation exposure in an infant and pregnancy exposure in a foetus) and 16 (3 serious; 13 nonserious) reporting exposure only during lactation were identified.

Cumulatively, 1,292 (572 medically confirmed and 720 medically unconfirmed) primary dose and 114 (36 medically confirmed and 78 medically unconfirmed) booster dose cases were retrieved by the search strategy for use in pregnancy/use in breastfeeding women.

Of these 1,406 cases, 113 did not meet the criteria for inclusion in this section (cases of congenital anomalies reported in patients and not related to pregnancy or lactation exposure). In 10 cases,

placebo was given and Ad26.COV2.S was not involved. Additionally, 118 cases reported maternal exposure to vaccine >3 months before pregnancy, 23 reported paternal exposure to vaccine >2 weeks before pregnancy, and 1 case reported vaccination after pregnancy. Nine cases concerned multiple patients without individual patient identifiers and 3 were duplicate cases. These 277 cases are not discussed further.

Of the remaining 1,129 cumulative cases received, 129 were reported from Janssen Sponsored Clinical Studies, 28 from Janssen Supported Clinical Studies, and 923 from post-marketing sources (including spontaneous and solicited sources).

Cumulatively, 978 cases reporting exposure during pregnancy (including 4 reporting lactation exposure along with pregnancy exposure in the same baby and 2 reporting lactation exposure in an infant and pregnancy exposure in a foetus) and 151 reporting exposure only during lactation were identified.

Pregnancy

Janssen Sponsored Clinical Studies Cases

During the reporting period of 25 February 2022 to 24 August 2022, 65 cases reporting use in pregnancy were retrieved from Janssen Sponsored Clinical Studies. Of the 65 cases, 27 were reported from VAC31518COV3001, 13 each from both VAC31518COV2004 and VAC31518COV3009, 6 from VAC31518COV3003, 5 from VAC31518COV2008, and 1 from VAC31518COV1001. Of these 65 cases, the most frequently reported countries/territories of origin were Brazil (n=19), followed by the US (n=17), and South Africa (n=13). These cases concerned 57 females, 6 males, and 2 did not report sex. The age range was from 19 to 43 years for maternal cases and 0 to 0.14 years for baby cases.

Cumulatively, 128 (39 serious and 89 nonserious) cases from Janssen Sponsored Clinical Studies reporting exposure during pregnancy were identified (65 were reported from VAC31518COV3001, 34 from VAC31518COV3009, 15 from VAC31518COV2004, 8 from VAC31518COV3003, 5 from VAC31518COV2008 and 1 from VAC31518COV1001). These 128 cases comprised 106 maternal, 4 paternal exposure, and 18 linked to maternal cases (9 linked baby and 9 linked paternal). Where reported, maternal age ranged from 19 to 46 years with mean and median of 31.3 and 31.5 years, respectively.

The 128 cumulative cases reported 110 unique pregnancies, of which 46 reported an outcome as follows: live birth without congenital anomaly (n=23), spontaneous abortion (n=14, including 1 case of missed abortion), elective abortion (n=4; 2 due to congenital anomalies: skeletal dysplasia and unspecified anomaly), ectopic pregnancy (n=2), intrauterine death, live birth with congenital anomaly (tracheomalacia), and still birth (n=1 case each). Of the 14 cases reporting the outcome of spontaneous abortion, there were 7 with exposure before conception/pregnancy, 4 with exposure during the first trimester of pregnancy, and for the remaining 3 timing of vaccine exposure was not reported.

Janssen Supported Clinical Studies Cases

During the reporting period of 25 February 2022 to 24 August 2022, 8 cases reporting use in pregnancy were retrieved from Janssen Supported Clinical Studies. Of the 8 cases, 5 were reported from VAC31518COV3012, 2 from VAC31518COV2012, and 1 from VAC31518COV3021. The reported countries/territories of origin were South Africa (n=6) and Thailand (n=2). All cases concerned adult females aged from 25 to 53 years.

Cumulatively, 28 (27 serious and 1 nonserious) cases from Janssen Supported Clinical Studies reporting exposure during pregnancy were identified (24 from VAC31518COV3012 and 2 each from VAC31518COV2012 and VAC31518COV3021). All cases reported maternal exposure; where reported, maternal age ranged from 24 to 53 years with mean and median of 34.5 and 34.0 years, respectively.

The 28 cumulative cases reported 28 unique pregnancies, of which 5 reported an outcome: live birth without congenital anomaly (n=3; in 1 case neonatal death in a "severely premature" baby was reported 4 days after delivery), and spontaneous abortion (n=2). Of the 2 cases reporting the outcome of spontaneous abortion, in 1 of them, the trimester of exposure was not reported and in the other the abortion occurred 21 days after the mother received the booster dose of Ad26.COV2.S at gestation of 13 weeks and 6 days.

Post-marketing Sources (Including Spontaneous and Solicited Sources) Cases

During the reporting period of 25 February 2022 to 24 August 2022, 348 (133 serious and 215 nonserious) post-marketing (including spontaneous and solicited sources) cases reporting exposure during pregnancy were retrieved. Of the 348 cases, 221 were from the following solicited sources: COVID-19 Vaccines International Pregnancy Exposure Registry (C-VIPER, n=219), and PPSOTH004154 and SafeVac 2.0 smartphone app (n=1 each).

Of these 348 post-marketing cases, the most frequently reported countries/territories of origin were the Philippines (n=145), followed by South Africa (n=95), and the US (n=89). These 348 cases comprised 269 maternal, 38 baby, and 41 linked to maternal cases (27 linked baby, 13 booster, and 1 paternal). Where reported, maternal age ranged from 18 to 53 years with mean and median of 29.9 and 30.0 years, respectively.

Cumulatively, 822 (279 serious and 543 nonserious) post-marketing cases reporting exposure during pregnancy were identified. Of the 822 cases, 535 were from the following solicited sources: C-VIPER (n=531), PPSOTH004154 (n=2), COVID-19 LIM (noncompany study) and SafeVac 2.0 (n=1 each).

Of these 822 post-marketing cases, the most frequently reported countries/territories of origin were the US (n=437), followed by the Philippines (n=158), and South Africa (n=114). These 822 cases comprised 698 maternal, 2 baby, and 122 linked to maternal cases (104 linked baby, 16 linked booster, and 2 paternal). Where reported, maternal age ranged from 18 to 53 years with mean and median of 31.2 and 32.0 years, respectively.

The frequency distribution of additional AE in mother cases and baby AEs in baby cases reported in post-marketing cases during the interval reporting period and cumulatively are presented in Table 79 and Table 80 below, respectively. A single case may contain more than 1 event.

Table 79: Frequency Distribution of Additional Adverse Events in Mother Cases Reporting Exposure During Pregnancy With the Use of Ad26.COV2.S

MedDRA PTs	Number of Additional Adverse Events Reported During the Reporting Period[a]		Number of Additional Adverse Events Received Cumulatively[a]	
	Serious	Nonserious	Serious	Nonserious
Labour pain	37	19	42	19
Pain in extremity	3	43	5	138
Myalgia	4	37	8	101
Pyrexia	1	37	7	106
Chills	4	31	12	122
Headache	2	33	6	111
Fatigue	1	30	7	141
Malaise	1	25	8	93
Arthralgia	1	13	2	45
Vaccination site pain	8	5	8	5
COVID-19	1	9	2	21
Back pain	9	0	9	3
Injection site swelling	0	9	0	16
Nausea	0	9	3	37
Dyspnoea	2	3	6	5
Gestational hypertension	3	2	5	6

Key: COVID-19=Corona Virus Disease 2019; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term

a: The MedDRA PTs with a frequency ≥5 have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event.

Table 80: Frequency Distribution of Additional Adverse Events in Baby Cases Reporting Exposure During Pregnancy With the Use of Ad26.COV2.S

MedDRA PTs	Number of Additional Adverse Events Reported During the Reporting Period[a]		Number of Additional Adverse Events Received Cumulatively[a]	
	Serious	Nonserious	Serious	Nonserious
COVID-19	2	8	5	9
Large for dates baby	2	7	3	15
Ear infection	1	4	1	4
Gastrooesophageal reflux disease	2	3	5	4
Neonatal dyspnoea	5	0	10	0
Ankyloglossia congenital	4	0	4	0
Gastroenteritis	2	2	2	2
Premature baby	4	0	5	0
Blood glucose decreased	2	1	2	1
Breech presentation	3	0	4	0
Cough	0	3	0	3
Jaundice neonatal	2	1	4	3
Pyrexia	1	2	1	4

Table 80: Frequency Distribution of Additional Adverse Events in Baby Cases Reporting Exposure During Pregnancy With the Use of Ad26.COV2.S

MedDRA PTs	Number of Additional Adverse Events Reported During the Reporting Period[a]		Number of Additional Adverse Events Received Cumulatively[a]	
	Serious	Nonserious	Serious	Nonserious
Weight gain poor	1	2	1	2
Acoustic stimulation tests abnormal	1	1	1	1
Death	2	0	2	0
Oral candidiasis	2	0	2	0
Rhinorrhoea	0	2	0	2
Small for dates baby	1	1	1	1
Suspected COVID-19	0	2	0	2

Key: COVID-19=Corona Virus Disease 2019; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term

a: The MedDRA PTs with a frequency ≥2 have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event.

The 348 interval cases reported 307 unique pregnancies of which 275 were prospective and 32 were retrospectively reported. The outcomes reported in these 307 pregnancies (including pregnancy ongoing or outcome not reported) are provided in Table 81.

Table 81: Unique Pregnancy Outcomes in Post-marketing Cases Reporting Exposure During Pregnancy With Ad26.COV2.S During the Reporting Period 25 February 2022 to 24 August 2022 (Cases=307)

Pregnancy Outcomes	Number of Pregnancy Outcomes
Live birth without congenital anomalies	69[a]
Ongoing pregnancy	17
Spontaneous abortion	16[a,b]
Live birth with congenital anomalies	9
Ectopic pregnancy	3
Blighted ovum	2
Intrauterine death	1
Maternal death	1
NR	191
Total	**309**

Key: AE=Adverse Event; NR=Not Reported

a: One case reported twins with different pregnancy outcomes; hence, 2 outcomes have been presented for 1 unique case in their respective outcome category.

b: One case reported twins; hence, 2 outcomes have been presented for 1 unique case.

Cumulatively, 822 cases reported 700 unique pregnancy cases, of which 614 were prospective and 86 were retrospectively reported. In 200 of the 700 unique pregnancy cases, an outcome was reported, as presented in Table 82. Of the 200 unique pregnancy cases, 15 reported the following congenital anomalies: ankyloglossia congenital (n=4), macrocephaly (n=2), buried penis syndrome, cardiac septal defect, cleft lip, congenital hydrocephalus, external auditory canal atresia, heart disease congenital, high foetal head, Kabuki make-up syndrome, labial tie, palatal disorder, pyelocaliectasis, pyloric stenosis, renal aplasia, spina bifida, ventricular septal defect (n=1 each). In addition to the 200 unique pregnancy cases presented in Table 82, and

2 reported unspecified congenital anomalies (foetal disorder and foetal malformation) and 2 reported other baby AE (foetal hypokinesia and ultrasound foetal abnormal) detected in an ongoing pregnancy or in a pregnancy with no reported outcome.

Table 82: Summary Table of Unique Pregnancy Outcomes Cumulatively through 24 August 2022; Cases=200 Unique Pregnancies

Pregnancy Outcome	Prospective Cases Number				Retrospective Cases Number				Total
	Timing of Exposure in Pregnancy				Timing of Exposure in Pregnancy				
	Before Conception	First Trimester	After First Trimester	Unknown	Before Conception	First Trimester	After First Trimester	Unknown	
Ectopic Pregnancy	0	0	0	0	3	0	0	2	**5**
Spontaneous Abortion[a]	0	6[a]	0	0	10[b]	19	0	21[c,d]	**56**
Stillbirth With Foetal Defects	0	0	0	0	0	0	1	0	**1**
Stillbirth Without Foetal Defects	0	0	0	0	0	1	0	0	**1**
Live Birth With Congenital Anomaly	0	5	7[e]	0	0	0	1	1	**14**
Live Birth Without Congenital Anomaly[a]	2	37[f,g]	59[h,i]	2	0	3[j]	9	11[k]	**123**
Intrauterine Death	0	0	0	0	0	0	1	0	**1**
Maternal Death	0	1	0	0	0	0	0	0	**1**
Blighted Ovum	0	0	0	0	0	0	0	2	**2**
Total[l]	**2**	**49**	**66**	**2**	**13**	**23**	**12**	**37**	**204**

Key: AE=Adverse Event; n=Number of Pregnancy Outcomes

a: One case [redacted] reported spontaneous abortion in a twin pregnancy at first trimester. Hence, the count for spontaneous abortion for this case is included as n=2.

b: One case [redacted] reported spontaneous abortion with AE in a twin pregnancy. Hence, the count for spontaneous abortion is included as n=2.

Table 82: Summary Table of Unique Pregnancy Outcomes Cumulatively through 24 August 2022; Cases=200 Unique Pregnancies

Pregnancy Outcome	Prospective Cases Number				Retrospective Cases Number				Total
	Timing of Exposure in Pregnancy				Timing of Exposure in Pregnancy				
	Before Conception	First Trimester	After First Trimester	Unknown	Before Conception	First Trimester	After First Trimester	Unknown	

c: One case ([redacted]) reported the patient experienced a miscarriage at an unknown time after vaccination, either before conception, or in the first trimester. The patient reportedly experienced 3 additional miscarriages approximately every 28 days over the subsequent 3 months. This is recorded as 1 pregnancy outcome.

d: One case ([redacted]) reported an incomplete abortion.

e: One case ([redacted]) reported exposure to the Pfizer vaccine in the first trimester/periconception and a booster dose of Ad26.COV2.S in the third trimester (31.4 weeks of gestational age).

f: Following an initial dose in the first trimester, 1 case ([redacted]) reported that the patient was administered a booster dose of Ad26.COV2.S in the third trimester (36.3 weeks of gestational age). Neonatal jaundice occurred post administration of the booster dose.

g: Following an initial dose in the first trimester, 2 cases ([redacted]) and ([redacted]) reported that the patient was administered a booster dose of Ad26.COV2.S in the third trimester (32 weeks and 33.6 weeks of gestational age, respectively) and 1 case ([redacted]) reported that the patient was administered a booster dose of Ad26.COV2.S in the second trimester (14.9 weeks of gestational age).

h: One case ([redacted]) reported that the patient was administered Ad26.COV2.S in the second and third trimesters (initial at 14.9 weeks and booster at 35.2 weeks of gestational age).

i: One case ([redacted]) reported live birth with AE in a twin pregnancy. Hence, the count for the live birth without congenital anomaly for this case is included as n=2.

j: One case ([redacted]) reported that the patient was administered Ad26.COV2.S in the first and third trimesters (initial at 8.7 weeks and booster at 35.4 weeks of gestational age).

k: One case ([redacted]) reported deep vein thrombosis in a baby at the age of 13.7 weeks.

l: A single case may report more than 1 pregnancy outcome due to twin pregnancy or multiple pregnancies within a case.

Use in Breastfeeding Women

Janssen Sponsored Clinical Studies Cases

During the reporting period of 25 February 2022 to 24 August 2022, 1 case reporting use in a breastfeeding woman was retrieved from a Janssen Sponsored Clinical Study. This nonserious case reported 1 nonserious event from VAC31518COV3001. The country/territory of origin was [redacted] Age and sex were unspecified in this case. The event included exposure via breast milk (n=1) with unknown outcome.

Janssen Supported Clinical Studies Cases

During the reporting period no cases reporting use in breastfeeding women were retrieved from Janssen Supported Clinical Studies.

Post-marketing Sources (Including Spontaneous and Solicited Sources) Cases

The administration of Ad26.COV2.S to breastfeeding women was reported in 15 (3 medically confirmed and 12 medically unconfirmed) cases in the reporting period. Of these 15 cases, none came from solicited sources, and 3 were serious and 12 were nonserious. All 15 were unique lactation cases: 9 were nonserious baby (3 had baby AEs and are presented in Table 83) and 6 were maternal without associated baby AEs. Of the 6 maternal cases, 3 were serious reporting the following serious AEs in addition to maternal exposure during breastfeeding: arthralgia, dizziness, headache, injection site pain, myalgia, pyrexia, and tachycardia.

A frequency distribution of AEs experienced by babies in the interval reporting period and cumulatively are presented below in Table 83.

Table 83: Frequency Distribution of Baby Adverse Events in Cases Reporting Exposure During Breastfeeding With Ad26.COV2.S During the Reporting Period 25 February 2022 to 24 August 2022

MedDRA PTs	Number of Additional Adverse Events Reported During the Reporting Period[a]		Number of Additional Adverse Events Received Cumulatively[a]	
	Serious	Nonserious	Serious	Nonserious
Adverse event	0	1	0	1
Apathy	0	1	0	2
Asthenia	0	1	0	1
Decreased appetite	0	1	0	2
Diarrhoea	0	1	0	2
Fatigue	0	1	0	1
Illness	0	1	0	1
Pyrexia	0	1	0	12
Somnolence	0	1	0	3
Vomiting	0	1	0	3

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

a: The additional adverse events were sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022).

Cumulatively, administration of Ad26.COV2.S to a lactating mother followed by breastfeeding of a baby was reported in 150 (53 medically confirmed and 97 medically unconfirmed) cases. Of these 150 cases, 3 came from solicited sources (2 from social media and 1 from COVID-19 LIM), and 12 were serious and 138 nonserious. The 12 serious cases were comprised of 7 maternal, 3 baby and 2 linked mother cases. These 150 cases reported 135 unique lactation cases. These 150 cases were comprised of 118 baby, 17 maternal, and 15 linked mother cases. Of the 118 baby cases, baby AEs were reported in 26 (2 of which were serious). These 26 cases reported 60 additional events (3 serious, 57 nonserious) with pyrexia as the most frequently reported (n=12).

A review of these cases, including demographics, concomitant medications, concurrent conditions/medical history, outcome, and seriousness, is consistent with what is currently known about the missing information of use during pregnancy and use in breastfeeding women.

Booster Dose

Cumulatively, 100 (28 medically confirmed and 72 medically unconfirmed) cases reported as booster were identified. Of these cases, 39 were heterologous and 61 were homologous. These cases are discussed in the above section along with the primary dose cases.

Of the 100 cumulative cases reported as booster, 18 were reported from Janssen Sponsored Clinical Studies (VAC31518COV3001 [n=15], VAC31518COV3009 [n=2] and VAC31518COV3003 [n=1]), 1 from a Janssen Supported Clinical Study (VAC31518COV3021), and 81 from post-marketing sources (including spontaneous and solicited sources).

A cumulative booster dose CIOMS II LL is presented in Appendix 6.10.

Literature ICSR

One ICSR literature case was received and reviewed during the reporting period of 25 February 2022 to 24 August 2022. The case concerned a 30-year-old female (gravida 1, para 0) who received Ad26.COV2.S in the second trimester of pregnancy. The patient's past medical history was notable only for heterozygous factor V Leiden deficiency (not currently on treatment) and the patient had no obstetric issues. The patient experienced an all-over body rash 1 week after vaccination. Approximately 2 weeks later, the patient presented with neurological symptoms of left facial weakness, with significant bifacial paresis and bilateral hand paraesthesia. The facial diplegia variant of GBS was diagnosed; lumbar puncture demonstrated elevated cerebrospinal fluid protein and nerve conduction study found evidence of a diffuse sensorimotor demyelinating polyneuropathy. The patient fully recovered to baseline 4 weeks after presentation and at 40 weeks and 5 days gestation, gave birth to a healthy baby via normal spontaneous vaginal delivery without complications. No new information was identified for the missing information of use during pregnancy.

Discussion

No new critical safety information was identified during the reporting period for the missing information of use during pregnancy and use in breastfeeding women. In addition, a COVID-19 Vaccines International Pregnancy Exposure Registry (C-VIPER) an annual report covering the period 01 June 2021 to 31 May 2022 concluded that no safety concerns were identified for either mother or child in cases reporting pregnancy (see Appendix 9.6, C-VIPER).

Conclusion

Based on the evaluation of the cases, and review of safety from other sources, the information is consistent with the information known about use during pregnancy and lactation. The Company will continue to closely monitor the use of Ad26.COV2.S during pregnancy and lactation.

16.3.5.2. Use in Breastfeeding Women

Information on use in breastfeeding women is covered in the section above, Section 16.3.5.1., Use During Pregnancy.

16.3.5.3. Use in Immunocompromised Patients

Introduction

According to the cRMP (version 4.0; dated 09 December 2021), use in immunocompromised patients is considered missing information for Ad26.COV2.S. Characterisation of this risk is provided in Section 16.4, Characterisation of Risks.

Methods

The Company global safety database was searched for medically confirmed and medically unconfirmed cases received during this reporting period and cumulatively which were coded to the search criteria provided in Appendix 5.

Results/Discussion

Primary Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 1,005 (582 medically confirmed and 423 medically unconfirmed) initial, primary dose cases reporting use in immunocompromised patients were identified. Of these 1,005 cases, 714 were serious and 291 were nonserious and reported a total of 4,239 events (2,441 serious; 1,798 nonserious).

Of these 1,005 primary dose cases received during the interval reporting period, 275 were reported from Janssen Sponsored Clinical Studies, 95 from Janssen Supported Clinical Studies, and 635 from post-marketing sources (including spontaneous and solicited).

Cumulatively, 8,043 (3,435 medically confirmed and 4,608 medically unconfirmed) primary dose cases reporting use in immunocompromised patients were identified. Of these cases, 4,299 were

serious and 3,744 were nonserious and reported a total of 45,033 events (18,200 serious; 26,833 nonserious).

Of the 8,043 cumulative primary dose cases received, 838 were reported from Janssen Sponsored Clinical Studies, 407 from Janssen Supported Clinical Studies, and 6,798 from post-marketing sources (including spontaneous and solicited cases).

Janssen Sponsored Clinical Studies Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 275 initial, primary dose cases reporting use in immunocompromised patients were retrieved from Janssen Sponsored Clinical Studies. Of the 275 cases, 179 were from VAC31518COV3001, 82 from VAC31518COV3009, 9 from VAC31518COV2008, 3 from VAC31518COV1001, and 2 from VAC31518COV3005. These 275 cases reported 328 events (291 serious; 37 nonserious). Of these 275 cases, the most frequently reported countries/territories of origin (n≥29) were the US (n=151), followed by South Africa (n=31) and Brazil (n=29). These cases concerned 156 males and 119 females. The age range was from 19 to 87 years.

The most frequently reported events in these retrieved cases (≥5) included thrombocytopenia (n=25), pneumonia (n=10), deep vein thrombosis (n=6), and asthma and osteoarthritis (n=5 each). The mean and median TTO were 355.5 and 359 days, respectively. Where reported (n=317), the outcomes were resolved (n=168), not resolved (n=62), resolving (n=50), fatal (n=27), and resolved with sequelae (n=10). Of note, platelet counts in clinical trials were being monitored as a protocol mandated procedure. Most of the reported events of thrombocytopenia were nonserious (22 out of 25) with latencies ranging between 244 and 507 days post initial dose.

Janssen Supported Clinical Studies Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 95 initial, primary dose cases reporting use in immunocompromised patients were retrieved from Janssen Supported Clinical Studies. Of the 95 cases, 50 were from VAC31518COV3012, 36 from VAC31518COV3021, and 9 from VAC31518COV2012. These 95 cases reported 98 events (95 serious; 3 nonserious). Of these 95 cases, the reported countries/territories of origin were South Africa (n=86), followed by Thailand (n=9). These cases concerned 79 females and 16 males. The age range was from 23 to 79 years.

The most frequently reported events in these retrieved cases (≥2) included COVID-19 (n=92) and gastroenteritis (n=2). The mean and median TTO were 309.8 and 349.5 days, respectively. Where reported (n=97), the outcomes were resolved (n=83), fatal (n=11), and resolving (n=3).

Post-marketing Sources (Including Spontaneous and Solicited) Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 635 post-marketing sources (including spontaneous and solicited), initial, primary dose cases reporting use in

immunocompromised patients were retrieved. These 635 initial, post-marketing, primary dose cases reported 3,813 events (2,055 serious; 1,758 nonserious).

Cumulatively, 6,798 (2,190 medically confirmed and 4,608 medically unconfirmed) post-marketing, primary dose cases reporting use in immunocompromised patients were identified. Of these cases, 3,190 were serious and 3,608 were nonserious and reported a total of 43,559 events (16,905 serious; 26,654 nonserious).

An overview of these cases is presented in Table 84 below.

Table 84: Characteristics of Post-marketing, Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Use In Immunocompromised Patients

Case Characteristics		Number of Cases Received During the Interval Reporting Period=635	Number of Cases Received Cumulatively=6,798
Sex	Female	401	4,587
	Male	202	2,036
	NR	32	175
Age (Years)[a]	<18	2	41
Minimum: 14	18 to 35	111	1,100
Maximum: 90	36 to 50	166	1,675
Mean: 50	51 to 64	192	2,177
Median: 51	≥65	91	1,232
	Adult	25	99
	Elderly	10	25
	Foetus	0	1
	NR	38	448
Sources	Spontaneous	589	6,310
	Clinical study (noninterventional; solicited)	36	466
	Clinical study (noninterventional; unsolicited)	6	14
	Interventional clinical trial	4	8
Country/Territory[b]	United States	325	4,611
	Spain	36	120
	France	30	207
	Canada	29	37
	Greece	28	43
	South Africa	24	37
	Germany	23	128
	Brazil	19	91
	Poland	16	61
	Austria	15	64
	Belgium	13	57
	Netherlands	12	653
	Slovenia	10	18

Table 84: Characteristics of Post-marketing, Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Use In Immunocompromised Patients

Case Characteristics		Number of Cases Received During the Interval Reporting Period=635	Number of Cases Received Cumulatively=6,798
	Switzerland	10	34
Event Characteristics		**Number of Events=3,813**	**Number of Events=43,559**
Seriousness (Event Level)[c]	Serious	2,055	16,905
	Nonserious	1,758	26,654
Outcome (Event Level)[c]	Not resolved	1,501	17,002
	Resolved	781	11,859
	Fatal	353	1,447
	Resolving	263	4,164
	Resolved with sequelae	25	156
	NR	890	8,931

Key: NR=Not Reported
a: The calculation was based on the current reporting period (25 February 2022 to 24 August 2022). Age group was presented for cases where age was not reported.
b: Countries/Territories with frequency ≥10 were presented in decreasing order for the current reporting period (25 February 2022 to 24 August 2022).
c: Seriousness and outcome have been presented for all the events. A single case may report more than 1 event.

Of these 635 post-marketing, initial, primary dose cases, the most frequently reported countries/territories of origin (n≥29) were the US (n=325), followed by Spain (n=36), and Canada (n=29). These cases concerned 401 females, 202 males, and 32 did not report sex. The age range was from 14 to 90 years.

The frequency distribution of relevant medical history PTs reported in the 635 cases is presented in Table 85 below. A single case may contain more than 1 relevant medical history.

Table 85: Frequency Distribution of Relevant Medical History PTs Involving the Use of Ad26.COV2.S and Reporting Use in Immunocompromised Patients

Medical History	Count of Medical History PTs During the Reporting Period[a]	Count of Medical History PTs Cumulatively
Drug hypersensitivity	239	2,962
Asthma	80	942
Seasonal allergy	74	1,207
Food allergy	46	1,189
Rheumatoid arthritis	45	251
Hypersensitivity	44	505
Crohn's disease	34	141
Psoriasis	30	193
Autoimmune thyroiditis	25	206
Allergy to animal	22	301
Psoriatic arthropathy	18	89
Colitis ulcerative	16	83
Anaphylactic reaction	13	74

Table 85: Frequency Distribution of Relevant Medical History PTs Involving the Use of Ad26.COV2.S and Reporting Use in Immunocompromised Patients

Medical History	Count of Medical History PTs During the Reporting Period[a]	Count of Medical History PTs Cumulatively
Mite allergy	13	233
Multiple sclerosis	12	108
Allergy to arthropod sting	11	126
Multiple allergies	10	121

Key: PT=Preferred Term

a: The medical history PTs of interest with frequency ≥10 have been presented by decreasing order for the reporting period (25 February 2022 to 24 August 2022).

b: A single case may report more than 1 relevant medical history.

The frequency distribution of the MedDRA PTs reported in post-marketing, primary dose cases is presented in Table 86 below. A single case may contain more than 1 event.

Table 86: Frequency of MedDRA PTs in Post-marketing, Primary Dose Cases Reporting Use in Immunocompromised Patients With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Headache	27	79	290	1,668
Pyrexia	21	68	236	1,202
Fatigue	24	56	209	1,361
COVID-19	28	34	126	114
Vaccination failure	60	0	271	0
Pain	13	41	118	789
Suspected COVID-19	4	47	18	109
Pain in extremity	16	34	174	737

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term; SARS-CoV-2=Severe Acute Respiratory Syndrome Coronavirus-2

a: The MedDRA PTs with a frequency ≥50 have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event.

The most frequently reported events in these retrieved cases (n≥50) included headache (n=106), pyrexia (n=89), fatigue (n=80), COVID-19 (n=62), vaccination failure (n=60), pain (n=54), suspected COVID-19 (n=51), and pain in extremity (n=50). The mean and median TTO were 84.0 and 12 days, respectively. Where reported (n=2,923), the outcomes were not resolved (n=1,501), resolved (n=781), fatal (n=353), resolving (n=263), and resolved with sequelae (n=25).

As presented in Table 87 below, the majority of the MedDRA PTs referring to vaccination failure occurred in cases which did not meet the case definition of lack of efficacy (presented in Section 15.5, Vaccination Failure, Lack of Efficacy/Effectiveness).

Table 87: Distribution of MedDRA PTs by Case Definition Criteria of Vaccination Failure

Case Definition Criteria	Number of PTs		
	COVID-19	Vaccination failure	Suspected COVID-19
Confirmed vaccination failure (medically confirmed, TTO>14 days and positive COVID-19 testing)	4 serious 0 nonserious	0	0
Suspected vaccination failure (medically confirmed, TTO>14 days and COVID-19 testing not reported)	0	0	0
Case definition not met	24 serious 34 nonserious	60 serious 0 nonserious	4 serious 47 nonserious

Key: COVID-19=Coronavirus Disease-2019; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term; TTO=Time to Onset

Fatal Post-marketing Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 24 post-marketing, initial, primary dose fatal cases with 353 fatal events were retrieved. The most frequently reported fatal events (n≥5) were death (n=12), COVID-19 (n=8), acute respiratory failure and COVID-19 pneumonia (n=7 each), SARS-CoV-2 test positive (n=6); and condition aggravated, dyspnoea, and pneumonia (n=5 each). Most of the fatal events occurred in the context of COVID-19 infection.

Booster Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 375 (103 medically confirmed and 272 medically unconfirmed) initial cases reported as booster were identified. There were 221 serious and 154 nonserious cases and reported a total of 1,308 events (430 serious; 878 nonserious). Of these cases, 220 were heterologous and 155 were homologous.

Of these 375 cases reported as booster during the interval, 19 were reported from Janssen Sponsored Clinical Studies, 12 from Janssen Supported Clinical Studies, and 344 from post-marketing sources (including spontaneous and solicited).

Cumulatively, 595 (179 medically confirmed and 416 medically unconfirmed) cases reported as booster were identified. Of these cases, 320 were serious and 275 were nonserious and reported a total of 2,435 events (776 serious; 1,659 nonserious). Of these cases, 318 were homologous and 277 were heterologous.

Of the 595 cumulative booster dose cases received, 40 were reported from Janssen Sponsored Clinical Studies, 14 from Janssen Supported Clinical Studies, and 541 from post-marketing sources (including spontaneous and solicited cases).

A cumulative booster dose CIOMS II LL is presented in Appendix 6.11.

Janssen Sponsored Clinical Studies Booster Dose Cases

During the interval reporting period of 25 February 2022 to 24 August 2022, 19 initial cases reported as booster were retrieved from Janssen Sponsored Clinical Studies. Of the 19 cases, 18 were from VAC31518COV3001 and 1 from VAC31518COV3005. These 19 cases reported 27 events (20 serious; 7 nonserious). Of these 19 cases, the most frequently reported countries/territories of origin (n≥3) were the US (n=9), followed by South Africa (n=4) and Brazil (n=3). These cases concerned 12 females and 7 males. The age range was from 32 to 76 years.

The most frequently reported events in these retrieved cases (n≥2) included thrombocytopenia (n=7), and chronic obstructive pulmonary disease and diverticulitis (n=2 each). The mean and median TTO were 149.4 days and 142.0 days, respectively. The reported outcomes were resolved (n=18), resolving (n=6), not resolved (n=2), and resolved with sequelae (n=1). Of note, platelet counts in clinical trials were being monitored as a protocol mandated procedure. All the reported events of thrombocytopenia were nonserious with latencies ranging between 0 to 76 days post-vaccination.

Janssen Supported Clinical Studies Booster Dose Cases

During the interval reporting period of 25 February 2022 to 24 August 2022, 12 initial cases reported as booster were retrieved from Janssen Supported Clinical Studies. Of the 12 cases, 11 were from VAC31518COV3021 and 1 from VAC31518COV2012. These 12 cases reported 12 events (11 serious; 1 nonserious). For these 12 cases, the reported countries/territories of origin were South Africa (n=11) and Thailand (n=1). These cases concerned 11 females and 1 male. The age range was from 25.5 to 83 years.

The reported event was COVID-19 in all retrieved cases. The mean and median TTO were 167.1 days and 162.0 days, respectively. The reported outcomes were resolved (n=10) and fatal (n=2).

Post-marketing Sources (Including Spontaneous and Solicited) Booster Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 344 post-marketing sources (including spontaneous and solicited), initial cases reported as booster were retrieved. These 344 post-marketing, initial, booster dose cases reported 1,269 events (399 serious; 870 nonserious).

Cumulatively, 541 (125 medically confirmed and 416 medically unconfirmed) post-marketing, cases reported as boosters were identified. Of these cases, 291 cases were serious and 250 were nonserious and reported a total of 2,364 events (735 serious; 1,629 nonserious).

An overview of these cases is presented in Table 88 below.

Table 88: Characteristics of Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Use in Immunocompromised Patients

Case Characteristics		Number of Cases Received During the Interval Reporting Period=344	Number of Cases Received Cumulatively=541
Sex	Female	212	351
	Male	112	167
	NR	20	23
Age (Years)[a]	<18	1	1
Minimum: 13	18 to 35	45	63
Maximum: 85	36 to 50	85	124
Mean: 52.2	51 to 64	110	190
Median: 53	≥65	67	113
	Adult	10	13
	Elderly	1	3
	NR	25	34
Sources	Spontaneous	294	476
	Clinical study (noninterventional; solicited)	27	41
	Clinical study (noninterventional; unsolicited)	23	24
Country/Territory[b]	United States	236	393
	Brazil	58	63
	Canada	21	36
	Germany	6	10
	South Africa	5	6
	Austria	4	8
	Philippines	3	4
	Spain	3	4
	Belgium	2	2
	France	2	3
Classification	Heterologous	216	272
	Homologous	128	269
Event Characteristics		**Number of Events=1,269**	**Number of Events=2,364**
Seriousness (Event Level)[c]	Serious	399	735
	Nonserious	870	1,629
Outcome (Event Level)[c]	Not resolved	309	607
	Resolved	233	513
	Resolving	131	236
	Fatal	17	24
	Resolved with sequelae	4	8
	NR	575	976

Key: NR=Not Reported

a: The calculation was based on the current reporting period (25 February 2022 to 24 August 2022). Age group was presented for cases where age was not reported.

Table 88: Characteristics of Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Use in Immunocompromised Patients

Case Characteristics	Number of Cases Received During the Interval Reporting Period=344	Number of Cases Received Cumulatively=541

b: Countries/Territories with frequency ≥2 were presented in decreasing order for the current reporting period (25 February 2022 to 24 August 2022).
c: Seriousness and outcome have been presented for all the events. A single case may report more than 1 event.

Of these 344 post-marketing, initial cases reported as booster, the most frequently reported countries/territories of origin (n≥21) were the US (n=236), followed by Brazil (n=58) and Canada (n=21). These cases concerned 212 females and 112 males. The age range was from 13 to 85 years.

The frequency distribution of relevant medical history PTs reported in the 344 cases is presented in Table 89 below. A single case may contain more than 1 relevant medical history.

Table 89: Frequency Distribution of Relevant Medical History PTs in Post-marketing Cases Reported as Booster Dose Involving the Use of Ad26.COV2.S and Reporting Use in Immunocompromised Patients

Medical History	Count of Medical History PTs During the Reporting Period[a]	Count of Medical History PTs Cumulatively
Drug hypersensitivity	168	294
Asthma	45	66
Food allergy	44	74
Hypersensitivity	41	60
Rheumatoid arthritis	39	51
Crohn's disease	25	35
Seasonal allergy	21	46
Ankylosing spondylitis	15	17
Psoriasis	11	20
Psoriatic arthropathy	11	15
Colitis ulcerative	10	20
Autoimmune thyroiditis	7	11
Immunodeficiency	6	11
Rubber sensitivity	6	12
Allergy to arthropod sting	5	9
Iodine allergy	5	7
Multiple allergies	5	15
Multiple sclerosis	5	6
Rhinitis allergic	5	7

Key: PT=Preferred Term
a: The medical history PTs of interest with frequency ≥5 have been presented by decreasing order for the reporting period (25 February 2022 to 24 August 2022).
b: A single case may report more than 1 relevant medical history.

The frequency distribution of the MedDRA PTs reported in post-marketing cases reported as booster is presented in Table 90 below. A single case may contain more than 1 event.

Table 90: Frequency of MedDRA PTs in Post-marketing Cases Reported as Booster Dose With the Use of Ad26.COV2.S and Reporting Use in Immunocompromised Patients

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Vaccination failure	113	0	136	0
COVID-19	10	102	15	113
Off label use	0	93	0	126
Suspected COVID-19	3	57	3	73
Inappropriate schedule of product administration	0	50	0	79
Pyrexia	3	20	9	44
Pain in extremity	4	16	10	41
Headache	1	18	8	41
Pain	3	16	6	35
Arthralgia	2	16	4	22
Fatigue	3	13	5	38
Dysgeusia	0	15	0	18
Chills	0	12	1	30
Diarrhoea	1	10	1	18
Feeling abnormal	0	10	2	24
Nausea	1	9	8	23

Key: COVID-19=Coronavirus Disease 2019; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term

a: The MedDRA PTs with a frequency ≥10 have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event.

The most frequently reported events in these retrieved cases (n≥50) included vaccination failure (n=113), COVID-19 infection (n=112), off label use (n=93), suspected COVID-19 infection (n=60), and inappropriate schedule of product administration (n=50). The mean and median TTO were 142.3 days and 64 days, respectively. Where reported (n=694), the outcomes were not resolved (n=309), resolved (n=233), resolving (n=131), fatal (n=17), and resolved with sequelae (n=4).

As presented in Table 91 below, the majority of MedDRA PTs referring to vaccination failure were reported in cases which did not meet the case definition for lack of efficacy (See Section 15.5, Vaccination Failure, Lack of efficacy/Effectiveness).

Table 91: Distribution of MedDRA PTs by Case Definition Criteria of Vaccination Failure

Case Definition Criteria	Number of PTs		
	Vaccination failure	COVID-19	Suspected COVID-19
Confirmed vaccination failure (medically confirmed, TTO>14 days and positive COVID-19 testing)	10 serious 0 nonserious	4 serious 0 nonserious	0 serious 2 nonserious

Table 91: Distribution of MedDRA PTs by Case Definition Criteria of Vaccination Failure

Case Definition Criteria	Number of PTs		
	Vaccination failure	COVID-19	Suspected COVID-19
Suspected vaccination failure (medically confirmed, TTO>14 days and COVID-19 testing not reported)	0	0	0
Case definition not met	103 serious 0 nonserious	6 serious 102 nonserious	3 serious 55 nonserious

Key: COVID-19=Coronavirus Disease-2019; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term; TTO=Time to Onset

Fatal Post-marketing Booster Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 6 initial, fatal cases reported as booster with 17 fatal events were retrieved. The reported fatal events were acute respiratory distress syndrome and cough (n=2 each), and asthenia, COVID-19 infection, COVID-19 pneumonia, decreased appetite, diarrhoea, dysarthria, dyspnoea, gait inability, GBS, oxygen saturation decreased, paraesthesia, pyrexia, and vision blurred (n=1 each).

Literature ICSR

ICSR literature cases received during the reporting period of 25 February 2022 to 24 August 2022 were reviewed, No new information was identified on the use of Ad26.COV2.S in immunocompromised patients.

Discussion

Based on the evaluation of the cases, and review of safety from other sources, the nature of reported AEs in immunocompromised patients is consistent with the known safety profile of Ad26.COV2.S and with what is expected in this patient population. The warnings and precaution section of the CCDS states that immunocompromised persons including individuals receiving immunosuppressant therapy, may have a diminished immune response to Ad26.COV2.S.

Conclusion

The Company will continue to closely monitor use in immunocompromised patients as missing information.

16.3.5.4. Use in Patients With Autoimmune or Inflammatory Disorders

Introduction

Use in patients with autoimmune or inflammatory disorders is considered missing information for Ad26.COV2.S according to the cRMP (version 4.0; dated 09 December 2021). Characterisation of this risk is provided in Section 16.4, Characterisation of Risks.

Cumulative information on flares of autoimmune disorders was reviewed in the previous PBRER for Ad26.COV2.S covering the reporting period of 25 August 2021 to 24 February 2022. Based on review of the information, the PRAC in its assessment report (EMEA/H/C/PSUSA/00010916/202202) concluded that there are no indications of a causal association between the Ad26.COV2.S vaccine and flares of autoimmune disorders with the exception of ITP which is already covered in the SmPC. The suggestion by the MAH that "Use of Ad26.COV2.S in subjects with Autoimmune or Inflammatory Disorders" remains an area of missing information was endorsed by PRAC. In addition to the ongoing additional pharmacovigilance activities to gather more data in this population (2 observational post authorisation safety studies, VAC31518COV4003 and VAC31518COV4001), PRAC considered it sufficient that this area is followed via routine pharmacovigilance.

Methods

The Company global safety database was searched for medically confirmed and medically unconfirmed cases received during this reporting period and cumulatively which were coded to the search criteria provided in Appendix 5.

Results/Discussion

Primary Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 685 (437 medically confirmed and 248 medically unconfirmed) initial, primary dose cases reporting use in patients with autoimmune or inflammatory disorders were identified. Of these 685 cases, 490 were serious and 195 were nonserious and reported a total of 2,712 events (1,653 serious; 1,059 nonserious).

Of these 685 primary dose cases received during the interval reporting period, 226 were reported from Janssen Sponsored Clinical Studies, 71 from Janssen Supported Clinical Studies, and 388 from post-marketing sources (including spontaneous and solicited).

Cumulatively, 4,658 (2,490 medically confirmed and 2,168 medically unconfirmed) primary dose cases reporting use in patients with autoimmune or inflammatory disorders were identified. Of these cases 2,938 were serious and 1,720 were nonserious and reported a total of 23,678 events (11,974 serious; 11,704 nonserious).

Of the 4,658 cumulative primary dose cases received, 702 were reported from Janssen Sponsored Clinical Studies, 489 from Janssen Supported Clinical Studies, and 3,467 from post-marketing sources (including spontaneous and solicited cases).

Janssen Sponsored Clinical Studies Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 226 initial, primary dose cases reporting use in patients with autoimmune or inflammatory disorders were retrieved from Janssen Sponsored Clinical Studies. Of the 226 cases, 142 were from VAC31518COV3001, 70 from VAC31518COV3009, 10 from VAC31518COV2008, 2 from VAC31518COV1001, and 1 each from VAC31518COV3005 and VAC31518COV3003. These 226 cases

reported 273 events (235 serious; 38 nonserious). Of these 226 cases, the most frequently reported countries/territories of origin (n≥20) were the US (n=111), followed by Brazil (n=33) and South Africa (n=20). These cases concerned 136 females and 90 males. The age range was from 24 to 93 years.

The most frequently reported events (≥5) included thrombocytopenia (n=26), osteoarthritis (n=10), cellulitis and deep vein thrombosis (n=6 each), and diverticulitis (n=5). The mean and median TTO were 357.0 and 367.0 days, respectively. Where reported (n=269), the outcomes were resolved (n=151), resolving (n=44), not resolved (n=29), fatal (n=27), and resolved with sequelae (n=18). Of note, monitoring of platelet levels was a protocol mandated procedure in Company-sponsored clinical trials as part of the TTS AESI which artificially incremented the number of thrombocytopenia cases in CTs. Twenty-four of the 26 reported events of thrombocytopenia were nonserious with a latency ranging between 57 and 498 days post-primary dose, none were considered related by the investigator.

Janssen Supported Clinical Studies Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 71 initial, primary dose cases reporting use in patients with autoimmune or inflammatory disorders were retrieved from Janssen Supported Clinical Studies. Of the 71 cases, 38 were from VAC31518COV3021, 31 from VAC31518COV3012, and 2 from VAC31518COV2012. These 71 cases reported 72 events (70 serious; 2 nonserious). The countries/territories of origin in these 71 cases were from South Africa (n=69) and Thailand (n=2). These cases concerned 53 females and 18 males. The age range was from 29 to 89 years.

The events reported in these 71 cases included COVID-19 (n=70), followed by gastroenteritis and maternal exposure before pregnancy (n=1 each). Latencies ranged from 23 to 473 days post-primary dose with mean and median TTO of 326.9 and 354.5 days, respectively. Where reported (n=71), the outcomes were resolved (n=66) and fatal (n=5).

Post-marketing Sources (Including Spontaneous and Solicited) Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 388 post-marketing sources (including spontaneous and solicited), initial, primary dose cases reporting use in patients with autoimmune or inflammatory disorders were retrieved. These 388 post-marketing, initial, primary dose cases reported 2,367 events (1,348 serious; 1,019 nonserious).

Cumulatively, 3,467 (1,299 medically confirmed and 2,168 medically unconfirmed) post-marketing, primary dose cases reporting use in patients with autoimmune or inflammatory disorders were identified. Of these cases, 1,880 were serious and 1,587 were nonserious and reported a total of 22,289 events (10,759 serious; 11,530 nonserious).

An overview of these cases is presented in Table 92 below.

Table 92: Characteristics of Post-marketing, Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Use in Patients With Autoimmune or Inflammatory Disorders

Case Characteristics		Number of Cases Received During the Interval Reporting Period=388	Number of Cases Received Cumulatively=3,467
Sex	Female	235	2,318
	Male	126	1,031
	NR	27	118
Age (Years)[a]	<18	2	5
Minimum: 14	18 to 35	46	322
Maximum: 90	36 to 50	90	714
Mean: 52.4	51 to 64	127	1,222
Median: 54.0	≥65	60	846
	Adult	22	71
	Elderly	11	22
	NR	30	265
Sources	Spontaneous	348	3,300
	Clinical study (noninterventional; solicited)	34	154
	Clinical study (noninterventional; unsolicited)	5	12
	Interventional clinical trial	1	1
Country/Territory[b]	United States	188	2,410
	Spain	42	103
	Canada	27	34
	France	24	168
	Germany	14	82
	Greece	12	27
	Brazil	11	50
	South Africa	11	24
	Austria	9	35
	Poland	8	43
	Croatia	6	36
	Belgium	5	22
Event Characteristics		**Number of Events=2,367**	**Number of Events=22,289**
Seriousness (Event Level)[c]	Serious	1,348	10,759
	Nonserious	1,019	11,530
Outcome (Event Level)[c]	Not resolved	736	8,739
	Resolved	515	5,075
	Fatal	290	1,439
	Resolving	160	1,819
	Resolved with sequelae	6	60
	NR	660	5,157

Key: NR=Not Reported

a: The calculation was based on the current reporting period (25 February 2022 to 24 August 2022). Age group was presented for cases where age was not reported.

Table 92: Characteristics of Post-marketing, Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Use in Patients With Autoimmune or Inflammatory Disorders

Case Characteristics	Number of Cases Received During the Interval Reporting Period=388	Number of Cases Received Cumulatively=3,467

b: Countries/Territories with frequency ≥5 were presented in decreasing order for the current reporting period (25 February 2022 to 24 August 2022).
c: Seriousness and outcome have been presented for all the events. A single case may report more than 1 event.

Of these 388 post-marketing, initial, primary dose cases, the most frequently reported countries/territories of origin (n≥27) were the US (n=188), followed by Spain (n=42) and Canada (n=27). These cases concerned 235 females, 126 males, and 27 did not report sex. The age range was from 14 to 90 years.

The frequency distribution of the MedDRA PTs reported in post-marketing, primary dose cases is presented in Table 93 below. A single case may contain more than 1 event.

Table 93: Frequency of MedDRA PTs reported in Post-marketing, Primary Dose Cases Reporting Use in Patients With Autoimmune or Inflammatory Disorders With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Headache	11	50	143	634
Pyrexia	13	48	130	468
Fatigue	14	37	106	562
COVID-19	21	18	110	58
Pain	10	28	69	380
Suspected COVID-19	4	27	17	51
Vaccination failure	31	0	162	0
Malaise	16	14	61	184
Myalgia	4	26	48	239
Nausea	5	24	67	261
Pain in extremity	7	22	86	357
Chills	5	21	54	335
Dyspnoea	16	9	152	121
Arthralgia	6	18	55	271
Dizziness	6	16	81	226
Condition aggravated	12	7	86	80
SARS-CoV-2 test positive	15	3	73	10
Asthenia	6	11	78	165
Thrombosis	17	0	172	0
Chest pain	12	4	92	65
Cough	8	7	50	67
Diarrhoea	3	11	28	132
Feeling abnormal	4	10	25	157
Death	13	0	82	0
Vomiting	9	4	59	102

Table 93: Frequency of MedDRA PTs reported in Post-marketing, Primary Dose Cases Reporting Use in Patients With Autoimmune or Inflammatory Disorders With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Back pain	3	9	33	72
Decreased appetite	3	9	20	71
Laboratory test	10	2	46	16
Vaccination site pain	0	12	4	43
Anticoagulant therapy	11	0	82	1
Gait disturbance	6	5	44	61
Injection site pain	0	11	11	212
Paraesthesia	3	8	46	120
Muscle spasms	2	8	14	62
Rash	2	8	21	83

Key: COVID-19=Coronavirus disease-2019; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term; SARS-CoV-2=Severe Acute Respiratory Syndrome Coronavirus-2

a: The MedDRA PTs with a frequency ≥10 have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event.

The most frequently reported events (n≥30) included headache and pyrexia (n=61 each), fatigue (n=51), COVID-19 (n=39), pain (n=38), suspected COVID-19 and vaccination failure (n=31 each), and malaise and myalgia (n=30 each). The mean and median TTO were 106.0 and 29.5 days, respectively. Where reported (n=1,707), the outcomes were not resolved (n=736), resolved (n=515), fatal (n=290), resolving (n=160), and resolved with sequelae (n=6).

The frequency distribution of relevant medical history PTs reported in the 388 cases is presented in Table 94 below. A single case may contain more than 1 relevant medical history PT.

Table 94: Frequency Distribution of Relevant Medical History PTs Involving the Use of Ad26.COV2.S and Reporting Use in Patients With Autoimmune or Inflammatory Disorders

Medical History	Count of Medical History PTs During the Reporting Period[a]	Count of Medical History PTs Cumulatively
Diabetes mellitus	53	700
Hypothyroidism	50	539
Rheumatoid arthritis	45	251
Crohn's disease	34	141
Psoriasis	30	193
Autoimmune thyroiditis	25	206
Arthritis	19	245
Psoriatic arthropathy	18	89
Colitis ulcerative	16	83
Multiple sclerosis	12	108
Ankylosing spondylitis	8	38

Table 94: Frequency Distribution of Relevant Medical History PTs Involving the Use of Ad26.COV2.S and Reporting Use in Patients With Autoimmune or Inflammatory Disorders

Medical History	Count of Medical History PTs During the Reporting Period[a]	Count of Medical History PTs Cumulatively
Systemic lupus erythematosus	7	98
Autoimmune hypothyroidism	6	11
Basedow's disease	6	46
Coeliac disease	6	66
Thyroid disorder	6	159
Autoimmune disorder	5	94
Sjogren's syndrome	5	46
Type 1 diabetes mellitus	5	85
Hyperthyroidism	4	45
Immune thrombocytopenia	4	29

Key: PT=Preferred Term

a: The medical history PTs of interest with frequency ≥4 have been presented by decreasing order for the reporting period (25 February 2022 to 24 August 2022).

b: A single case may report more than 1 relevant medical history.

Fatal Post-marketing Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 24 post-marketing, initial, primary dose fatal cases with 290 fatal events were retrieved. The most frequently reported fatal events (n≥5) were death (n=13, mostly in polymorbid patients in context of COVID-19 infection) and COVID-19 infection (n=5).

Booster Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 205 (71 medically confirmed and 134 medically unconfirmed) initial cases reported as booster were identified. There were 95 serious and 110 nonserious cases and reported a total of 661 events (222 serious; 439 nonserious). Of these cases, 103 were heterologous and 102 were homologous.

Of these 205 cases reported as booster during the interval, 15 were reported from Janssen Sponsored Clinical Studies, 7 from Janssen Supported Clinical Studies, and 183 from post-marketing sources (including spontaneous and solicited).

Cumulatively, 351 (130 medically confirmed and 221 medically unconfirmed) cases reported as booster were identified. Of these cases, 148 were serious and 203 were nonserious and reported a total of 1,373 events (407 serious; 966 nonserious). Of these cases, 217 were homologous and 134 were heterologous.

Of the 351 cumulative booster dose cases received, 34 were reported from Janssen Sponsored Clinical Studies, 9 from Janssen Supported Clinical Studies, and 308 from post-marketing sources (including spontaneous and solicited cases).

A cumulative booster dose CIOMS II LL is presented in Appendix 6.12.

Janssen Sponsored Clinical Studies Booster Dose Cases

During the interval reporting period of 25 February 2022 to 24 August 2022, 15 initial cases reported as booster were retrieved from Janssen Sponsored Clinical Studies. All cases were from VAC31518COV3001. These 15 cases reported 21 events (14 serious; 7 nonserious). The countries/territories of origin in these 15 cases were from the US (n=9), followed by Brazil (n=3), and Argentina, Colombia and Mexico (n=1 each). These cases concerned 9 females and 6 males. The age range was from 35 to 76 years.

The most frequently reported events (n≥2) included thrombocytopenia (n=5) and diverticulitis (n=2). The mean and median TTO were 167.3 and 142.0 days, respectively. Where reported (n=19), the outcomes were resolved (n=10), resolving (n=6), not resolved (n=2), and resolved with sequelae (n=1).

Janssen Supported Clinical Studies Booster Dose Cases

During the interval reporting period of 25 February 2022 to 24 August 2022, 7 initial cases reported as booster were retrieved from a Janssen Supported Clinical Study. All cases were from VAC31518COV3021. These 7 cases reported 7 serious events. The reported country/territory of origin for all 7 cases was South Africa. These cases concerned 5 females and 2 males. The age range was from 44 to 83 years.

All cases reported the event COVID-19. The mean and median TTO were 199.1 and 186.0 days, respectively. The outcomes reported were resolved (n=4) and fatal (n=3).

Post-marketing Sources (Including Spontaneous and Solicited) Booster Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 183 post-marketing sources (including spontaneous and solicited), initial cases reported as booster were retrieved. These 183 post-marketing, booster dose cases reported 633 events (201 serious; 432 nonserious).

Cumulatively, 308 (87 medically confirmed and 221 medically unconfirmed) post-marketing, cases reported as booster were identified. Of these cases, 130 were serious and 178 were nonserious and reported a total of 1,324 events (383 serious; 941 nonserious).

An overview of these post-marketing, booster dose cases is presented in Table 95 below.

Table 95: Characteristics of Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Use in Patients With Autoimmune or Inflammatory Disorders

Case Characteristics		Number of Cases Received During the Interval Reporting Period=183	Number of Cases Received Cumulatively=308
Sex	Female	114	200
	Male	62	98
	NR	7	10

Table 95: Characteristics of Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Use in Patients With Autoimmune or Inflammatory Disorders

Case Characteristics		Number of Cases Received During the Interval Reporting Period=183	Number of Cases Received Cumulatively=308
Age (Years)[a] **Minimum: 20** **Maximum: 88** **Mean: 54.5** **Median: 56.0**	18 to 35	22	30
	36 to 50	36	56
	51 to 64	59	109
	≥65	46	81
	Adult	9	13
	Elderly	1	2
	NR	10	17
Country/Territory[b]	United States	100	186
	Brazil	44	47
	Canada	19	34
	Austria	5	8
	South Africa	3	6
	France	2	3
	Germany	2	6
	Philippines	2	2
	Spain	2	3
Sources	Spontaneous	135	245
	Clinical study (noninterventional; solicited)	24	38
	Clinical study (noninterventional; unsolicited)	24	25
Classification	Heterologous	101	132
	Homologous	82	176
Event Characteristics		**Number of Events=633**	**Number of Events=1,324**
Seriousness (Event Level)[c]	Nonserious	432	941
	Serious	201	383
Outcome (Event Level)[c]	Not resolved	130	330
	Resolved	124	284
	Resolving	69	102
	Fatal	13	17
	Resolved with sequelae	0	4
	NR	297	587

Key: NR=Not Reported

a: The calculation was based on the current reporting period (25 February 2022 to 24 August 2022). Age group was presented for cases where age was not reported.

b: Countries/Territories with frequency ≥2 were presented in decreasing order for the current reporting period (25 February 2022 to 24 August 2022).

c: Seriousness and outcome have been presented for all the events. A single case may report more than 1 event.

Of these 183 post-marketing, initial cases reported as booster, the most frequently reported countries/territories of origin (n≥19) were the US (n=100), followed by Brazil (n=44) and Canada (n=19). These cases concerned 114 females, 62 males, and 7 did not report sex. The age range was from 20 to 88 years.

The frequency distribution of the MedDRA PTs reported in post-marketing cases reported as booster is presented in Table 96 below. A single case may contain more than 1 event.

Table 96: Frequency of MedDRA PTs reported in Post-marketing Cases Reported as Booster Dose With the Use of Ad26.COV2.S and Reporting Use in Patients With Autoimmune or Inflammatory Disorders

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Off label use	0	70	0	107
COVID-19	6	44	9	49
Vaccination failure	31	0	37	0
Inappropriate schedule of product administration	0	29	0	62
Suspected COVID-19	1	22	1	27
Pain	2	11	5	24
Pyrexia	2	10	5	25
Arthralgia	1	10	2	17
Fatigue	5	6	6	26
Pain in extremity	1	10	5	22
Headache	1	6	3	22
Chills	1	5	1	17
Dyspnoea	3	3	4	5
Influenza	0	6	0	9
Malaise	1	5	3	11
Anticoagulant therapy	5	0	7	0
Chest pain	3	2	7	8
Dysgeusia	0	5	0	6
Injection site pain	0	5	0	10
Nausea	1	4	7	8
Peripheral swelling	0	5	3	5
SARS-CoV-2 test positive	2	3	4	5

Key: COVID-19=Coronavirus disease 2019; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term; SARS-CoV-2=Severe Acute Respiratory Syndrome Coronavirus-2

a: The MedDRA PTs with a frequency ≥5 have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event.

The most frequently reported events (n>20) included off label use (n=70), COVID-19 (n=50), vaccination failure (n=31), inappropriate schedule of product administration (n=29), and suspected COVID-19 (n=23). The mean and median TTO were 140.8 and 73.0 days, respectively. Where reported (n=336), the outcomes were not resolved (n=130), resolved (n=124), resolving (n=69), and fatal (n=13).

The frequency distribution of relevant medical history PTs reported in the 183 initial cases is presented in Table 97 below. A single case may contain more than 1 relevant medical history PT. The most frequently reported medical history PTs referred to rheumatoid arthritis, Crohn's disease and diabetes mellitus.

Table 97: Frequency Distribution of Relevant Medical History PTs in Post-marketing Cases Reported as Booster Dose Involving the Use of Ad26.COV2.S and Reporting Use in Patients With Autoimmune or Inflammatory Disorders

Medical History	Count of Medical History PTs During the Reporting Period[a,b]	Count of Medical History PTs Cumulatively[b]
Rheumatoid arthritis	39	51
Crohn's disease	25	35
Diabetes mellitus	20	41
Ankylosing spondylitis	15	17
Hypothyroidism	15	28
Psoriasis	11	20
Psoriatic arthropathy	11	15
Colitis ulcerative	10	20
Arthritis	9	17
Autoimmune thyroiditis	7	11
Multiple sclerosis	5	6
Hyperthyroidism	4	5
Thyroid disorder	4	11
Uveitis	4	5
Autoimmune disorder	3	6
Myasthenia gravis	3	3
Coeliac disease	2	3
Immune system disorder	2	3
Lichen sclerosus	2	2
Neuropathy peripheral	2	7
Type 1 diabetes mellitus	2	4

Key: PT=Preferred Term

a: The medical history PTs of interest with frequency ≥2 have been presented by decreasing order for the reporting period (25 February 2022 to 24 August 2022).

b: A single case may report more than 1 relevant medical history.

Fatal Post-marketing Booster Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 4 initial, fatal cases reported as booster with 13 fatal events were retrieved. The reported fatal events were COVID-19 pneumonia (n=2), abdominal pain, arthritis, chills, decreased appetite, dysarthria, gait inability, Guillain-Barre syndrome, hyperthermia, malaise, paraesthesia, and vaccination failure (n=1 each).

Literature ICSR

ICSR literature cases received during the reporting period of 25 February 2022 to 24 August 2022 were reviewed, and no information was identified that would change the

characterisation of use of Ad26.COV2.S in patients with autoimmune and inflammatory conditions.

Conclusion

Based on the evaluation of the cases, and review of safety from other sources, the information is consistent with the information known about use in patients with autoimmune or inflammatory disorders. The Company will continue to closely monitor use of the vaccine in this subpopulation as missing information.

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

Introduction

According to the cRMP (version 4.0; dated 09 December 2021), use in frail patients with comorbidities (eg, chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders) is considered missing information for Ad26.COV2.S. Characterisation of this risk is provided in Section 16.4, Characterisation of Risks.

Methods

The Company global safety database was searched for medically confirmed and medically unconfirmed cases received during this reporting period and cumulatively which were coded to the search criteria provided in Appendix 5.

Results/Discussion

Primary Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 43 (36 medically confirmed and 7 medically unconfirmed) initial, primary dose cases reporting use in frail patients with comorbidities (eg, COPD, diabetes, chronic neurological disease, cardiovascular disorders) were identified. Of these 43 cases, 21 were serious and 22 were nonserious and reported a total of 75 events (47 serious; 28 nonserious).

Of these 43 primary dose cases received during the interval reporting period, 35 were reported from Janssen Sponsored Clinical Studies and 8 from post-marketing sources (including spontaneous and solicited). No cases were reported from Janssen Supported Clinical Studies.

Cumulatively, 205 (137 medically confirmed and 68 medically unconfirmed) primary dose cases reporting use in frail patients with comorbidities (eg, COPD, diabetes, chronic neurological disease, cardiovascular disorders) were identified. Of these cases, 97 were serious and 108 were nonserious and reported a total of 619 events (304 serious; 315 nonserious).

Of the 205 cumulative primary dose cases received, 104 were reported from Janssen Sponsored Clinical Studies, 5 from Janssen Supported Clinical Studies, and 96 from post-marketing sources (including spontaneous and solicited cases).

Janssen Sponsored Clinical Studies Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 35 initial, primary dose cases reporting use in frail patients with comorbidities (eg, COPD, diabetes, chronic neurological disease, cardiovascular disorders) were retrieved from Janssen Sponsored Clinical Studies. Of the 35 cases, 25 were from VAC31518COV3001, 8 from VAC31518COV3009, and 2 from VAC31518COV3003. These 35 cases reported 44 events (24 serious; 20 nonserious). Of these 35 cases, the most frequently (n≥5) reported countries/territories of origin were Brazil (n=15), followed by Colombia and the US (n=5 each). These cases concerned 21 males and 14 females. The age range was from 32 to 79 years.

The most frequently reported events (≥4) included thrombocytopenia (n=15), deep vein thrombosis (n=7), and pulmonary embolism (n=4). The mean and median TTO were 407.2 and 426.0 days, respectively. The reported outcomes were resolved (n=21), not resolved and resolving (n=9 each), resolved with sequelae (n=3), and fatal (n=2).

Janssen Supported Clinical Studies Primary Dose Cases

There were no initial, primary dose cases retrieved from the search of the Company global safety database during the reporting period of 25 February 2022 to 24 August 2022.

Post-marketing Sources (Including Spontaneous and Solicited) Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 8 post-marketing sources (including spontaneous and solicited), initial, primary dose cases reporting use in frail patients with comorbidities (eg, COPD, diabetes, chronic neurological disease, cardiovascular disorders) were retrieved. These 8 post-marketing, initial, primary dose cases reported 31 events (23 serious; 8 nonserious).

Cumulatively, 96 (28 medically confirmed and 68 medically unconfirmed) post-marketing, primary dose cases reporting use in frail patients with comorbidities (eg, COPD, diabetes, chronic neurological disease, cardiovascular disorders) were identified. Of these cases, 49 were serious and 47 were nonserious and reported a total of 482 events (237 serious; 245 nonserious).

An overview of these cases is presented in Table 98 below.

Table 98: Characteristics of Post-marketing, Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Use in Frail Patients With Comorbidities (eg, COPD, Diabetes, Chronic Neurological Disease, Cardiovascular Disorders)

Case Characteristics		Number of Cases Received During the Interval Reporting Period=8	Number of Cases Received Cumulatively=96
Sex	Female	6	48
	Male	2	47
	NR	0	1
	18 to 35	1	10

Table 98: Characteristics of Post-marketing, Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Use in Frail Patients With Comorbidities (eg, COPD, Diabetes, Chronic Neurological Disease, Cardiovascular Disorders)

Case Characteristics		Number of Cases Received During the Interval Reporting Period=8	Number of Cases Received Cumulatively=96
Age (Years)[a] **Minimum: 32** **Maximum: 70** **Mean: 60.8** **Median: 66**	36 to 50	0	22
	51 to 64	1	18
	≥65	4	34
	Adult	1	1
	Elderly	0	1
	NR	1	10
Sources	Spontaneous	7	94
	Clinical study (noninterventional; solicited)	1	1
	Interventional clinical trial	0	1
Country/Territory	United States	7	57
	Germany	1	13
Event Characteristics		**Number of Events=31**	**Number of Events=482**
Seriousness (Event Level)[b]	Serious	23	237
	Nonserious	8	245
Outcome (Event Level)[b]	Not resolved	4	106
	Resolving	4	37
	Resolved	3	102
	Fatal	1	20
	NR	19	217

Key: COPD=Chronic Obstructive Pulmonary Disorder; NR=Not Reported

a: The calculation was based on the current reporting period (25 February 2022 to 24 August 2022). Age group was presented for cases where age was not reported.

b: Countries/Territories were presented in decreasing order for the current reporting period (25 February 2022 to 24 August 2022).

c: Seriousness and outcome have been presented for all the events. A single case may report more than 1 event.

For these 8 post-marketing, initial, primary dose cases, the countries/territories of origin were reported the US (n=7) and Germany (n=1). These cases concerned 6 females and 2 males. The age range was from 32 to 70 years.

The frequency distribution of the MedDRA PTs reported in post-marketing, primary dose cases is presented in Table 99 below. A single case may contain more than 1 event.

Table 99: Frequency of MedDRA PTs reported in Post-marketing, Primary Dose Cases Reporting Use in Frail Patients With Comorbidities (eg, COPD, Diabetes, Chronic Neurological Disease, Cardiovascular Disorders) With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Alopecia	0	1	0	2
Arthralgia	1	0	2	5
Arthritis infective	1	0	1	0
Asthenia	0	1	0	4
Blood test abnormal	1	0	1	0
Cataract	1	0	1	0
Chills	0	1	0	11
Chondrocalcinosis pyrophosphate	1	0	1	0
Compartment syndrome	1	0	1	0
Death	1	0	5	0
Decubitus ulcer	1	0	1	0
Exposure during pregnancy	0	1	0	1
Eye disorder	1	0	1	0
Eye infection	1	0	1	0
Fall	0	1	1	3
Haematochezia	1	0	1	0
Haemorrhage	1	0	2	0
Hepatic vascular thrombosis	1	0	1	0
Ill-defined disorder	1	0	1	0
Illness	0	1	0	2
Injury	0	1	0	1
Knee operation	1	0	1	0
Memory impairment	0	1	0	2
Muscle contracture	1	0	1	0
Musculoskeletal disorder	1	0	1	0
Musculoskeletal stiffness	1	0	1	0
Myocardial infarction	1	0	1	0
Pain	1	0	2	8
Sepsis	1	0	1	0
Speech disorder	1	0	3	1
Thrombosis	1	0	7	0

Key: COPD=Chronic Obstructive Pulmonary Disorder; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term

a: A single case may report more than 1 event.

The mean and median TTO were 56.0 and 26.5 days, respectively. Where reported (n=12), the outcomes were not resolved and resolving (n=4 each), resolved (n=3), and fatal (n=1).

The frequency distribution of relevant medical history PTs reported in the 8 cases is presented in Table 100 below.

Table 100: Frequency Distribution of Relevant Medical History PTs Involving the Use of Ad26.COV2.S and Reporting Use in Frail Patients With Comorbidities (eg, COPD, Diabetes, Chronic Neurological Disease, Cardiovascular Disorders)

Medical History	Count of Medical History PTs During the Reporting Period[a]	Count of Medical History PTs Cumulatively
Disability	3	31
Wheelchair user	2	13
Bedridden	1	11
Exercise lack of	1	23
Walking aid user	1	6

Key: COPD=Chronic Obstructive Pulmonary Disorder; PT=Preferred Term

a: The medical history PTs of interest have been presented by decreasing order for the reporting period (25 February 2022 to 24 August 2022).

Fatal Post-marketing Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 1 post-marketing, initial, primary dose fatal case with 1 fatal event was retrieved. The reported fatal event was death which occurred in a 67-year-old female with a past medical history of tobacco use, drug abuse, hepatitis C, oophroectomy, and benign ovarian tumour, and a concurrent conditions of rheumatoid arthritis, fibromyalgia, physical disability, liver disorder, and bedridden. The cause of death was not provided. The patient was hospitalised approximately 8 months post-vaccination for liver thrombosis. It was reported that the patient's "toxins" were high. Subsequently, the patient died 297 days post-vaccination. An autopsy was not performed. This case was medically unconfirmed.

Booster Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 14 (10 medically confirmed and 4 medically unconfirmed) initial cases reported as booster were identified. There were 2 serious and 12 nonserious cases and reported a total of 33 events (10 serious; 23 nonserious). Of these cases, 11 were homologous and 3 were heterologous.

Of these 14 cases reported as booster during the interval, 9 were reported from Janssen Sponsored Clinical Studies and 5 from post-marketing sources (including spontaneous and solicited). No cases were reported from Janssen Supported Clinical Studies.

Cumulatively, 40 (34 medically confirmed and 6 medically unconfirmed) cases reported as booster were identified. Of these cases, 4 were serious and 36 were nonserious and reported a total of 65 events (12 serious; 53 nonserious). Of these cases, 37 were homologous and 3 were heterologous.

Of the 40 cumulative cases reported as booster, 33 were reported from Janssen Sponsored Clinical Studies and 7 from post-marketing sources (including spontaneous and solicited cases). No cases were reported from Janssen Supported Clinical Studies.

A cumulative booster dose CIOMS II LL is presented in Appendix 6.13.

Janssen Sponsored Clinical Studies Booster Dose Cases

During the interval reporting period of 25 February 2022 to 24 August 2022, 9 initial cases reported as booster were retrieved from a Janssen Sponsored Clinical Study. All 9 cases were from VAC31518COV3001. These 9 cases reported 10 nonserious events. The reported countries/territories of origin in these 9 cases were the US (n=4), followed by Brazil (n=3), and Colombia and South Africa (n=1 each). These cases concerned 6 males and 3 females. None of the cases reported an age.

The reported events included thrombocytopenia (n=8) and hyperferritinaemia and platelet count decreased (n=1 each). The mean and median TTO were 122.5 and 28 days, respectively. Where reported (n=7), the outcome was resolving (n=4) and resolved (n=3).

Janssen Supported Clinical Studies Booster Dose Cases

There were no initial cases reported as booster which were retrieved from the search of the Company global safety database during the reporting period of 25 February 2022 to 24 August 2022.

Post-marketing Sources (Including Spontaneous and Solicited) Booster Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 5 post-marketing sources (including spontaneous and solicited), initial cases reported as booster were retrieved. These 5 post-marketing, booster dose cases reported 23 events (10 serious; 13 nonserious).

Cumulatively, 7 (1 medically confirmed and 6 medically unconfirmed) post-marketing cases reported as booster were identified. Of these cases, 3 were serious and 4 were nonserious and reported a total of 31 events (11 serious; 20 nonserious).

An overview of these post-marketing, booster dose cases is presented in Table 101 below.

Table 101: Characteristics of Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Use in Frail Patients With Comorbidities (eg, COPD, Diabetes, Chronic Neurological Disease, Cardiovascular Disorders)

Case Characteristics		Number of Cases Received During the Interval Reporting Period=5	Number of Cases Received Cumulatively=7
Sex	Male	3	5
	Female	2	2
Age (Years)[a]	36 to 50	1	2
Minimum: 48			
Maximum: 79	51 to 64	2	3
Mean: 62.0			
Median: 62.0	≥65	2	2
Country/Territory[b]	United States	3	5
	Austria	1	1
	Brazil	1	1

Table 101: Characteristics of Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Use in Frail Patients With Comorbidities (eg, COPD, Diabetes, Chronic Neurological Disease, Cardiovascular Disorders)

Case Characteristics		Number of Cases Received During the Interval Reporting Period=5	Number of Cases Received Cumulatively=7
Sources	Spontaneous	5	7
Classification	Homologous	4	6
	Heterologous	1	1
Event Characteristics		**Number of Events=23**	**Number of Events=31**
Seriousness (Event Level)[c]	Nonserious	13	20
	Serious	10	11
Outcome (Event Level)[c]	Resolved	8	15
	Not resolved	4	4
	Fatal	1	1
	NR	10	11

Key: COPD=Chronic Obstructive Pulmonary Disorder; NR=Not Reported
a: The calculation was based on the current reporting period (25 February 2022 to 24 August 2022).
b: Countries/Territories have been presented in decreasing order for the current reporting period (25 February 2022 to 24 August 2022).
c: Seriousness and outcome have been presented for all the events. A single case may report more than 1 event.

Of these 5 post-marketing, initial cases reported as booster, the reported countries/territories of origin were the US (n=3), followed by Austria and Brazil (n=1 each). These cases concerned 3 males and 2 females. The age range was from 48 to 79 years.

The frequency distribution of the MedDRA PTs reported in post-marketing cases reported as booster is presented in Table 102 below. A single case may contain more than 1 event.

Table 102: Frequency of MedDRA PTs reported in Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Use in Frail Patients With Comorbidities (eg, COPD, Diabetes, Chronic Neurological Disease, Cardiovascular Disorders)

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Deep vein thrombosis	2	0	2	0
Acute respiratory distress syndrome	1	0	1	0
Chest pain	0	1	0	1
COVID-19 pneumonia	1	0	1	0
Decreased appetite	0	1	0	1
Dependence on respirator	1	0	1	0
Dizziness	0	1	0	2
Dysgeusia	0	1	0	1
Dyspnoea	0	1	0	1
Gait disturbance	1	0	1	0
Hyperhidrosis	0	1	0	1

Table 102: Frequency of MedDRA PTs reported in Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Use in Frail Patients With Comorbidities (eg, COPD, Diabetes, Chronic Neurological Disease, Cardiovascular Disorders)

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Insomnia	0	1	0	1
Off label use	0	1	0	1
Palpitations	0	1	0	1
Performance status decreased	1	0	1	0
Pulmonary embolism	1	0	1	0
Rash	0	1	0	1
Subdural haematoma	1	0	1	0
Suspected COVID-19	0	1	0	1
Taste disorder	0	1	0	1
Vaccination failure	1	0	1	0
Vomiting	0	1	0	1

Key: COPD=Chronic Obstructive Pulmonary Disorder; COVID-19=Coronavirus Disease-2019; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term

a: The MedDRA PTs have been sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event.

The most frequently reported event was deep vein thrombosis (n=2). The mean and median TTO were 106.4 and 89.5 days, respectively. Where reported (n=13), the outcomes were resolved (n=8), not resolved (n=4), and fatal (n=1).

The frequency distribution of relevant medical history PTs reported in the 5 cases is presented in Table 103 below. A single case may contain more than 1 relevant medical history PT.

Table 103: Frequency Distribution of Relevant Medical History PTs Involving the Use of Ad26.COV2.S and Reporting Use in Frail Patients With Comorbidities (eg, COPD, Diabetes, Chronic Neurological Disease, Cardiovascular Disorders)

Medical History	Count of Medical History PTs During the Reporting Period[a,b]	Count of Medical History PTs Cumulatively[b]
Wheelchair user	2	2
Anorexia nervosa	1	1
Bedridden	1	1
Housebound	1	1
Walking aid user	1	2

Key: COPD=Chronic Obstructive Pulmonary Disorder; PT=Preferred Term

a: The medical history PTs of interest have been presented by decreasing order for the reporting period (25 February 2022 to 24 August 2022).

b: A single case may report more than 1 relevant medical history PT.

Fatal Post-marketing Booster Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 1 initial, fatal case reported as booster with 1 fatal event was retrieved. The reported fatal event was acute respiratory distress syndrome. This case concerned a 68-year-old male prison inmate with a history of cervical and supraspinal laminectomy and concurrent conditions of hypertension, mobility decreased, obesity, and wheelchair dependent who experienced shortness of breath and difficulty breathing approximately 79 days following a booster dose of Ad26.COV2.S. The patient was hospitalised due to hypoxia and was placed on mechanical ventilation. Acute respiratory failure was diagnosed as well as a right lower leg deep vein thrombosis and pulmonary embolism. Subsequently, the patient was diagnosed with a subdural hematoma. The patient's clinical course continued to deteriorate as the patient was diagnosed with bilateral pneumonia and tested positive for COVID-19 infection. The patient died from respiratory failure secondary to acute respiratory distress syndrome approximately 138 days following the booster dose of Ad26.COV2.S. It was unknown if an autopsy was performed.

Literature ICSR

No ICSR literature cases were received during the reporting period of 25 February 2022 to 24 August 2022.

Conclusion

Based on the evaluation of the cases, and review of safety from other sources, the information is consistent with the information known about use in frail patients with comorbidities (eg, COPD, diabetes, chronic neurological disease, cardiovascular disorders). The Company will continue to closely monitor use in frail patients with comorbidities (eg, COPD, diabetes, chronic neurological disease, cardiovascular disorders) as a missing information.

16.3.5.6. Interaction With Other Vaccines

Information on interaction with other vaccines has been presented in Section 15.3, Use With Concomitant Vaccination.

16.3.5.7. Long-term Safety

Introduction

According to the cRMP (version 4.0; dated 09 December 2021), long-term safety is considered missing information with the use of Ad26.COV2.S. Characterisation of this risk is provided in Section 16.4, Characterisation of Risks.

Methods

The Company global safety database was searched for medically confirmed and medically unconfirmed cases received during this reporting period and cumulatively, reporting long-term safety. For the purposes of this review, long-term safety was defined as cases with a latency of ≥6 months after the primary vaccination.

Results/Discussion

Primary Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 199 (160 medically confirmed and 39 medically unconfirmed) initial, primary dose cases with a latency of ≥6 months after the primary vaccination were identified. Of these 199 cases, 163 were serious and 36 were nonserious and reported a total of 316 events (187 serious; 129 nonserious).

Of these 199 primary dose cases received during the interval reporting period, 27 were reported from Janssen Sponsored Clinical Studies, 115 from Janssen Supported Clinical Studies, and 57 from post-marketing sources (including spontaneous and solicited).

Cumulatively, 437 (268 medically confirmed and 169 medically unconfirmed) primary dose cases with a latency of ≥6 months after the primary vaccination were identified. Of these cases, 264 were serious and 173 were nonserious and reported a total of 794 events (316 serious; 478 nonserious).

Of the 437 cumulative primary dose cases received, 66 were reported from Janssen Sponsored Clinical Studies, 162 from Janssen Supported Clinical Studies, and 209 from post-marketing sources (including spontaneous and solicited cases).

Janssen Sponsored Clinical Studies Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 27 initial, primary dose cases with a latency of ≥6 months after the primary vaccination were retrieved from Janssen Sponsored Clinical Studies. Of the 27 cases, 24 were from VAC31518COV3001, 2 from VAC31518COV1001, and 1 from VAC31518COV3009. These 27 cases reported 32 events (31 serious; 1 nonserious). Of these 27 cases, the most frequently reported countries/territories of origin (n≥9) were the US (n=11), followed by South Africa (n=9). These cases concerned 15 females and 12 males. The age range was from 30 to 84 years.

The events (n≥2) included cerebrovascular accident, diabetic ketoacidosis, head injury, and thrombocytopenia (n=2 each). The mean and median TTO were 458.0 and 448.5 days, respectively. The outcomes were fatal (n=10), resolved (n=9), resolving (n=7), and not resolved and resolved with sequelae (n=3 each).

Janssen Supported Clinical Studies Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 115 initial, primary dose cases with a latency of ≥6 months after the primary vaccination were retrieved from Janssen Supported Clinical Studies. Of the 115 cases, 112 were from VAC31518COV3021 and 3 from VAC31518COV3012. These 115 cases reported 116 events (115 serious; 1 nonserious). The country/territory of origin in all 115 cases was South Africa. These cases concerned 86 females and 29 males. The age range was from 24 to 89 years.

The events (n>100) included COVID-19 (n=114). The mean and median TTO were 368.2 and 375 days, respectively. Where reported (n=115), the outcomes were resolved (n=108), fatal (n=6), and resolving (n=1).

Post-marketing Sources (Including Spontaneous and Solicited) Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 57 post-marketing sources (including spontaneous and solicited), initial, primary dose cases with a latency of ≥6 months after the primary vaccination were retrieved. These 57 post-marketing, initial, primary dose cases reported 168 events (41 serious; 127 nonserious).

Cumulatively, 209 (40 medically confirmed and 169 medically unconfirmed) post-marketing, primary dose cases with a latency of ≥6 months after the primary vaccination were identified. Of these cases, 53 were serious and 156 were nonserious and reported a total of 546 events (96 serious; 450 nonserious).

An overview of these cases is presented in Table 104 below.

Table 104: Characteristics of Post-marketing, Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Long-term Safety

Case Characteristics		Number of Cases Received During the Interval Reporting Period=57	Number of Cases Received Cumulatively=209
Sex	Female	31	90
	Male	21	78
	NR	5	41
Age (Years)[a]	<18	0	1
Minimum: 25	18 to 35	8	26
Maximum: 76	36 to 50	13	29
Mean: 47.4	51 to 64	10	28
Median: 44.0	≥65	4	12
	Adult	1	5
	Elderly	1	1
	NR	20	107
Sources	Spontaneous	56	202
	Clinical study (noninterventional; solicited)	1	7
Country/Territory[b]	United States	20	129
	Germany	8	12
	Brazil	3	3
	Czech Republic	3	9
	Netherlands	3	4
Event Characteristics		**Number of Events=168**	**Number of Events=546**
Seriousness (Event Level)[c]	Nonserious	127	450
	Serious	41	96

Table 104: Characteristics of Post-marketing, Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Long-term Safety

Case Characteristics		Number of Cases Received During the Interval Reporting Period=57	Number of Cases Received Cumulatively=209
Outcome (Event Level)[c]	Not resolved	66	108
	Resolved	17	89
	Resolving	14	61
	Fatal	1	6
	Resolved with sequelae	0	2
	NR	70	280

Key: NR=Not Reported
a: The calculation was based on the current reporting period (25 February 2022 to 24 August 2022). Age group was presented for cases where age was not reported.
b: Countries/Territories with frequency ≥3 were presented in decreasing order for the current reporting period (25 February 2022 to 24 August 2022).
c: Seriousness and outcome have been presented for all the events. A single case may report more than 1 event.

Of these 57 post-marketing, initial, primary dose cases, the most frequently reported countries/territories of origin (n≥8) were the US (n=20), followed by Germany (n=8). These cases concerned 31 females, 21 males, and 5 did not report sex. The age range was from 25 to 76 years.

The frequency distribution of the MedDRA PTs reported in post-marketing, primary dose cases is presented in Table 105 below. A single case may contain more than 1 event.

Table 105: Frequency of MedDRA PTs in Post-marketing, Primary Dose Cases Reporting Long-term Safety With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Headache	0	5	1	32
Off label use	0	5	0	10
Pyrexia	2	3	5	37

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: The MedDRA PTs with a frequency ≥5 have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event.

The events (n≥5) included headache, off label use, and pyrexia (n=5 each). The mean and median TTO were 699.3 and 59.5 days, respectively. Where reported (n=98), the outcomes were not resolved (n=66), resolved (n=17), resolving (n=14), and fatal (n=1).

Fatal Post-marketing Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 1 post-marketing, initial, primary dose case with a fatal outcome was identified in the scientific literature. This case

concerned high levels of aspartate aminotransferase (AST) observed in hospitalised patients while being treated for the SARS-COV2 infection. The authors concluded that an increased AST level was an independent factor of death in the study population (n=250 patients with primary vaccination with Ad26.COV2.S) for which no specific medical history, concurrent conditions, concomitant medications, treatments, causes of death, or autopsy results were reported.

Booster Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 32 (8 medically confirmed and 24 medically unconfirmed) initial cases reported as booster were identified. There were 12 serious and 20 nonserious cases and reported a total of 86 events (15 serious; 71 nonserious). Of these cases, 19 were homologous and 13 were heterologous.

Of these 32 cases reported as booster during the interval, 1 was reported from a Janssen Sponsored Clinical Study, 2 from Janssen Supported Clinical Studies, and 29 from post-marketing sources (including spontaneous and solicited).

Cumulatively, 49 (11 medically confirmed and 38 medically unconfirmed) cases reported as booster were identified. Of these cases, 19 were serious and 30 were nonserious and reported a total of 153 events (29 serious; 124 nonserious). Of these cases, 30 were homologous and 19 were heterologous.

Of the 49 cumulative cases reported as booster, 1 was reported from a Janssen Sponsored Clinical Study, 4 from Janssen Supported Clinical Studies, and 44 from post-marketing sources (including spontaneous and solicited cases).

A cumulative booster dose CIOMS II LL is presented in Appendix 6.14.

Janssen Sponsored Clinical Studies Booster Dose Cases

During the interval reporting period of 25 February 2022 to 24 August 2022, 1 initial case reported as booster was retrieved from a Janssen Sponsored Clinical Study. This case was reported from VAC31518COV3001 and concerned a 70-year-old male from [redacted], who experienced the serious events of diverticulitis, haematochezia, and melaena. The mean and median TTO were 391.7 and 398.0 days, respectively. The outcomes were reported as resolved (n=2) and resolved with sequelae (n=1).

Janssen Supported Clinical Studies Booster Dose Cases

During the interval reporting period of 25 February 2022 to 24 August 2022, 2 initial cases reported as booster were retrieved from Janssen Supported Clinical Studies. Both cases were from VAC31518COV3021 and reported 2 serious events. The reported country/territory of origin was South Africa for both cases. Both cases concerned females. The age was reported as 45 and 58.8 years.

The events included COVID-19 (n=2). The mean and median TTO was 371 days. The outcomes for the reported events were fatal (n=1) and resolved (n=1).

Post-marketing Sources (Including Spontaneous and Solicited) Booster Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 29 post-marketing sources (including spontaneous and solicited), initial cases reported as booster were retrieved. These 29 post-marketing, booster dose cases reported 81 events (10 serious; 71 nonserious).

Cumulatively, 44 (6 medically confirmed and 38 medically unconfirmed) post-marketing cases reported as booster were identified. Of these cases, 14 were serious and 30 were nonserious and reported a total of 146 events (22 serious; 124 nonserious).

An overview of these cases is presented in Table 106 below.

Table 106: Characteristics of Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Long-term Safety

Case Characteristics		Number of Cases Received During the Interval Reporting Period=29	Number of Cases Received Cumulatively=44
Sex	Female	19	26
	Male	7	13
	NR	3	5
Age (Years)[a] **Minimum: 18** **Maximum: 80** **Mean: 50.2** **Median: 52.0**	18 to 35	5	8
	36 to 50	3	4
	51 to 64	6	13
	≥65	3	4
	Adult	3	4
	Elderly	1	1
	NR	8	10
Country/Territory[b]	United States	12	24
	Brazil	6	7
	Germany	3	4
Sources	Spontaneous	20	31
	Clinical study (noninterventional; solicited)	5	7
	Clinical study (noninterventional; unsolicited)	4	6
Classification	Homologous	16	25
	Heterologous	13	19
Event Characteristics		**Number of Events=81**	**Number of Events=146**
Seriousness (Event Level)[c]	Nonserious	71	124
	Serious	10	22
Outcome (Event Level)[c]	Not resolved	13	24
	Resolved	10	28

Table 106: Characteristics of Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Long-term Safety

Case Characteristics		Number of Cases Received During the Interval Reporting Period=29	Number of Cases Received Cumulatively=44
	Resolving	3	13
	NR	55	81

Key: NR=Not Reported
a: The calculation was based on the current reporting period (25 February 2022 to 24 August 2022). Age group was presented for cases where age was not reported.
b: Countries/Territories with frequency ≥3 were presented in decreasing order for the current reporting period (25 February 2022 to 24 August 2022).
c: Seriousness and outcome have been presented for all the events. A single case may report more than 1 event.

Of these 29 post-marketing, initial cases reported as booster, the most frequently reported countries/territories of origin (n≥6) were the US (n=12), followed by Brazil (n=6). These cases concerned 19 females, 7 males, and 3 did not report sex. The age range was from 18 to 80 years.

The frequency distribution of the MedDRA PTs reported in post-marketing cases reported as booster is presented in Table 107 below. A single case may contain more than 1 event.

Table 107: Frequency of MedDRA PTs in Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Long-term Safety

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Off label use	0	9	0	17
Inappropriate schedule of product administration	0	6	0	14
COVID-19	0	5	0	7

Key: COVID-19: Coronavirus Disease-2019; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: The MedDRA PTs with a frequency ≥5 have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event.

The events (n≥5) included off label use (n=9), inappropriate schedule of product administration (n=6), and COVID-19 (n=5). The mean and median TTO were 148.4 and 31 days respectively. Where reported (n=26), the outcomes were not resolved (n=13), resolved (n=10), and resolving (n=3).

Fatal Post-marketing Booster Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 1 post-marketing case from Germany was retrieved which concerned an 18-year-old (sex unspecified) who died at an unspecified time following initial vaccination with Ad26.COV2.S and subsequent booster

vaccines: elasomeran (dose 2), CHADOX 1 NCOV-19 (dose 3), and tozinameran (dose 4). This case lacked relevant details concerning the patient's medical history/concurrent conditions, clinical course/treatment, concomitant medications, and cause of death. It was unknown if an autopsy was performed or if AEs following immunisation occurred with the above-named COVID-19 vaccines.

Literature ICSR

ICSR literature cases received during the reporting period of 25 February 2022 to 24 August 2022 were reviewed, and no information was identified that would change the characterisation of risk.

Discussion

Review of cases including demographics, concurrent conditions/medical history, concomitant medications, seriousness, and outcome received during the period covered by this report did not identify evidence suggestive of missing information of long-term safety being causally associated with Ad26.COV2.S.

Conclusion

Based on the evaluation of the cases, and review of safety from other sources, the information is consistent with the information known about long-term safety. The Company will continue to closely monitor long-term safety as missing information.

16.3.6. Adverse Events of Special Interest

As a part of its comprehensive routine pharmacovigilance activities to monitor safety of the Ad26.COV2.S vaccine use under US FDA EUA, and EMA conditional marketing authorisation (cMA), the MAH has initiated sequential inferential analyses to support and complement ongoing safety surveillance activities through retrospective analysis of observational claims data available. The objective of these analyses, referred to as RWDA is to assess the potential association between the occurrence of predefined AESIs and vaccination with the Ad26.COV2.S. Information on these analyses are found in Appendices 9.7.

In the PRAC FAR (procedure: EMEA/H/C/PSUSA/00010916/202202) for the Ad26.COV2.S PBRER dated 25 August 2021 to 24 February 2022, PRAC endorsed the discontinuation of presentation of the following separate AESI within the current and future PBRERs: Arrythmia, Heart failure, Diabetes mellitus, Autoimmune thyroiditis, and Thromboembolic and thrombotic events. In addition, Bell's palsy will no longer be presented in PBRERs, as PRAC has endorsed its classification as an ADR as "rare" (see Section 16.2.1.1.2, Facial Paralysis) and updates to the RSI documents.

16.3.6.1. Cardiac Disorders

16.3.6.1.1. Cardiac Inflammatory Disorder, Including Myocarditis and Pericarditis

Introduction

Cardiac inflammatory disorders, including myocarditis and pericarditis, is listed as an AESI in the cRMP, EU RMP, and the US Pharmacovigilance Plan (PVP).

Methods

The Company global safety database was searched for medically confirmed and medically unconfirmed cases received during this reporting period and cumulatively, which coded to the search criteria provided in Appendix 5.

An O/E analysis has been performed and information is presented in the O/E Analysis subsection below.

Results/Discussion

Primary Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 58 (33 medically confirmed and 25 medically unconfirmed) initial, primary dose cases reporting cardiac inflammatory disorders, including myocarditis and pericarditis, were identified. All 58 cases were serious and reported a total of 59 serious EOI.

Of these 58 primary dose cases received during the interval reporting period, 3 were reported from Janssen Sponsored Clinical Studies and 55 from post-marketing sources (including spontaneous and solicited cases). No cases were reported from Janssen Supported Clinical Studies.

Cumulatively, 411 (244 medically confirmed and 167 medically unconfirmed) primary dose cases reporting cardiac inflammatory disorders, including myocarditis and pericarditis, were identified. All 411 cases were serious and reported a total of 430 serious EOI.

Of the 411 cumulative primary dose cases received, 6 were reported from Janssen Sponsored Clinical Studies, 2 from Janssen Supported Clinical Studies, and 403 from post-marketing sources (including spontaneous and solicited cases).

Janssen Sponsored Clinical Studies Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 3 initial, primary dose cases reporting cardiac inflammatory disorders, including myocarditis and pericarditis, were retrieved from Janssen Sponsored Clinical Studies. Of the 3 cases, 1 each was reported from VAC31518COV3001, VAC31518COV3003, and VAC31518COV3009. These 3 cases reported 3 serious EOI. Of these 3 cases, the most frequently reported country/territory of origin (n≥2) was Brazil (n=2). All 3 cases concerned males. The age range was from 29 to 45 years.

The EOI included myocarditis (n=2) and myopericarditis (n=1). The mean and median TTO was 279.5 days. The outcomes were reported as resolved (n=2) and resolving (n=1).

Janssen Supported Clinical Studies Primary Dose Cases

There were no primary dose cases retrieved from the search of the Company global safety database during the reporting period of 25 February 2022 to 24 August 2022.

Post-marketing Sources (Including Spontaneous and Solicited) Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 55 post-marketing sources (including spontaneous and solicited), initial, primary dose cases reporting cardiac inflammatory disorders, including myocarditis and pericarditis, were retrieved. These 55 post-marketing, initial, primary dose cases reported 56 serious EOI.

Cumulatively, 403 (236 medically confirmed and 167 medically unconfirmed) post-marketing, primary dose cases reporting cardiac inflammatory disorders, including myocarditis and pericarditis, were identified. All 403 cases were serious and reported a total of 422 serious EOI.

An overview of these cases is presented in Table 108 below.

Table 108: Characteristics of Post-marketing, Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Cardiac Inflammatory Disorders, Including Myocarditis And Pericarditis

Case Characteristics		Number of Cases Received During the Interval Reporting Period=55	Number of Cases Received Cumulatively=403
Sex	Male	32	259
	Female	17	120
	NR	6	24
Age (Years)[a]	18 to 35	23	176
Minimum: 18	36 to 50	5	77
Maximum: 68	51 to 64	18	90
Mean: 40.9	≥65	1	27
Median: 39.0	Adult	1	4
	NR	7	29
Sources	Spontaneous	54	401
	Clinical study (noninterventional; solicited)	1	2
Country/Territory[b]	United States	19	193
	Germany	14	74
	Greece	5	10
	Poland	4	4
	South Africa	4	5
	Portugal	2	6
Event Characteristics		**Number of Events=56**	**Number of Events=422**

Table 108: Characteristics of Post-marketing, Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Cardiac Inflammatory Disorders, Including Myocarditis And Pericarditis

Case Characteristics		Number of Cases Received During the Interval Reporting Period=55	Number of Cases Received Cumulatively=403
Seriousness (Event Level)[c]	Serious	56	422
Outcome (Event Level)[c]	Not resolved	20	149
	Resolving	7	59
	Resolved	6	61
	Resolved with sequelae	6	12
	Fatal	3	17
	NR	14	124

Key: NR=Not Reported
a: The calculation was based on the current reporting period (25 February 2022 to 24 August 2022). Age group was presented for cases where age was not reported.
b: Countries/Territories with frequency ≥2 were presented in decreasing order for the current reporting period (25 February 2022 to 24 August 2022).
c: Seriousness and outcome have been presented for the events of interest. A single case may report more than 1 event of interest.

Of these 55 post-marketing, initial, primary dose cases, the most frequently reported countries/territories of origin (n≥14) were the US (n=19), followed by Germany (n=14). These cases concerned 32 males, 17 females, and 6 did not report sex. The age range was from 18 to 68 years.

The frequency distribution of the MedDRA PTs of interest reported in post-marketing, primary dose cases is presented in Table 109 below. A single case may contain more than 1 EOI.

Table 109: Frequency of MedDRA PTs of Interest in Post-marketing, Primary Dose Cases Reporting Cardiac Inflammatory Disorders, Including Myocarditis And Pericarditis With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Myocarditis	33	0	201	0
Pericarditis	16	0	186	0
Myopericarditis	6	0	29	0
Giant cell myocarditis	1	0	1	0

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: The MedDRA PTs of interest have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event of interest.

The EOI (n≥6) included myocarditis (n=33), pericarditis (n=16), and myopericarditis (n=6). The mean and median TTO were 54.6 days and 11.0 days respectively. Where reported (n=42), the

outcomes were not resolved (n=20), resolving (n=7), resolved and resolved with sequelae (n=6 each), and fatal (n=3).

Fatal Post-marketing Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 3 post-marketing, initial, primary dose fatal cases with 3 fatal EOI were retrieved. The fatal EOI was myocarditis in all 3 cases.

Two fatal cases reported a TTO within the risk window of 42 days. Of the 2 cases, 1 is medically confirmed and 1 is medically unconfirmed. Patient age is reported in 1 case. A 62-year-old male, with the TTO reported as 7 days post-vaccination in 1 case, and 40 days post-vaccination in the remaining case. The cause of death in these cases was reported as unspecified cause (n=1), and myocarditis, cardiac failure congestive (n=1). Both cases lacked essential information (medical history/concurrent conditions, autopsy report, clinical course details including diagnostic/laboratory workup, and concomitant medications) precluding any meaningful medical assessment.

One medically unconfirmed case reported the TTO outside of the risk window of 42 days. A 57-year-old female had a TTO reported as 73 days post-vaccination. The cause of death was reported as myocarditis. The case also lacked essential information (medical history/concurrent conditions, autopsy report, clinical course details including diagnostic/laboratory workup, and concomitant medications) precluding any meaningful medical assessment.

Booster Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 19 (6 medically confirmed and 13 medically unconfirmed) initial cases reported as booster were identified. All 19 cases were serious and reported a total of 20 serious EOI. Of these cases, 10 were heterologous and 9 were homologous.

Of these 19 cases reported as booster during the interval, 1 was reported from a Janssen Supported Clinical Study and 18 from post-marketing sources (including spontaneous and solicited). No cases were reported from Janssen Sponsored Clinical Studies.

Cumulatively, 24 (7 medically confirmed and 17 medically unconfirmed) cases reported as booster were identified. All 24 cases were serious and reported a total of 27 serious EOI. Of these cases, 12 were heterologous and 12 were homologous.

Of the 24 cumulative booster dose cases received, 1 was reported from a Janssen Supported Clinical Study and 23 from post-marketing sources (including spontaneous and solicited cases). No cases were reported from Janssen Sponsored Clinical Studies.

A cumulative booster dose CIOMS II LL is presented in Appendix 8.1.

Janssen Sponsored Clinical Studies Booster Dose Cases

There were no initial cases reported as booster which were retrieved from the search of the Company global safety database during the interval reporting period of 25 February 2022 to 24 August 2022.

Janssen Supported Clinical Studies Booster Dose Cases

During the interval reporting period of 25 February 2022 to 24 August 2022, 1 initial case reported as booster was retrieved from a Janssen Supported Clinical Study. This case was reported from VAC31518COV3021 and concerned a 23-year-old female from South Africa, who experienced a serious EOI of pericarditis. The TTO was reported as 3 days from the first dose, and the outcome was reported as resolved.

Post-marketing Sources (Including Spontaneous and Solicited) Booster Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 18 post-marketing sources (including spontaneous and solicited), initial cases reported as booster were retrieved. These 18 post-marketing booster dose cases reported 19 serious EOI.

Cumulatively, 23 (6 medically confirmed and 17 medically unconfirmed) post-marketing cases reported as booster were identified. All 23 cases were serious and reported a total of 26 serious EOI.

An overview of these cases is presented in Table 110 below.

Table 110: Characteristics of Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Cardiac Inflammatory Disorders, Including Myocarditis And Pericarditis

Case Characteristics		Number of Cases Received During the Interval Reporting Period=18	Number of Cases Received Cumulatively=23
Sex	Male	13	18
	Female	5	5
Age (Years)[a]	18 to 35	6	10
Minimum: 21	36 to 50	7	7
Maximum: 66	51 to 64	2	3
Mean: 39.8	≥65	1	1
Median: 43.0	Adult	1	1
	NR	1	1
Country/Territory[b]	Germany	6	8
	United States	5	8
	Austria	4	4
	Greece	2	2
	Hungary	1	1
Sources	Spontaneous	18	23

Table 110: Characteristics of Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Cardiac Inflammatory Disorders, Including Myocarditis And Pericarditis

Case Characteristics		Number of Cases Received During the Interval Reporting Period=18	Number of Cases Received Cumulatively=23
Classification	Heterologous	10	12
	Homologous	8	11
Event Characteristics		**Number of Events=19**	**Number of Events=26**
Seriousness (Event Level)[c]	Serious	19	26
Outcome (Event Level)[c]	Not resolved	5	7
	Resolved	5	5
	Resolving	2	3
	NR	7	11

Key: NR=Not Reported
a: The calculation was based on the current reporting period (25 February 2022 to 24 August 2022). Age group was presented for cases where age was not reported.
b: Countries/Territories were presented in decreasing order for the current reporting period (25 February 2022 to 24 August 2022).
c: Seriousness and outcome have been presented for the events of interest. A single case may report more than 1 event of interest.

Of these 18 post-marketing, initial cases reported as booster, the most frequently reported countries/territories of origin (n≥5) were Germany (n=6), followed by the US (n=5). These cases concerned 13 males and 5 females. The age range was from 21 to 66 years.

The frequency distribution of the MedDRA PTs of interest reported in post-marketing cases reported as booster is presented in Table 111 below. A single case may contain more than 1 EOI.

Table 111: Frequency of MedDRA PTs of Interest in Post-Marketing Cases Reported as Booster Dose With the Use of Ad26.COV2.S and Reporting Cardiac Inflammatory Disorders, Including Myocarditis And Pericarditis

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Myocarditis	11	0	17	0
Pericarditis	8	0	9	0

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: The MedDRA PTs of interest have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022).

The EOI included myocarditis (n=11) and pericarditis (n=8). The mean and median TTO were 50.5 and 11.0 days, respectively. Where reported (n=12), the outcomes were not resolved and resolved (n=5 each) and resolving (n=2).

Fatal Post-marketing Booster Dose Cases

There were no fatal cases reported as booster which were retrieved from the search of the Company global safety database during the interval reporting period of 25 February 2022 to 24 August 2022.

Literature ICSR

ICSR literature cases received during the reporting period of 25 February 2022 to 24 August 2022 were reviewed, and no information was identified that would change the characterisation of risk.

O/E Analysis Results

Appendix 7.1 contains the methodology used to calculate and perform the O/E analyses for the AESI. Results of the restricted O/E and sensitivity analysis are presented in Table 112.

Myocarditis

Table 112: Myocarditis: Restricted O/E and Sensitivity Analysis Results (Cumulative Through 24 August 2022)

		Restricted 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	Female	18 to 29	4.00	2.25	(0.61, 5.75)	16.33	(4.45, 41.81)
		30 to 39	4.00	1.25	(0.34, 3.19)	5.57	(1.52, 14.27)
		40 to 49	4.00	1.16	(0.32, 2.98)	4.63	(1.26, 11.86)
		50 to 64	4.00	0.82	(0.22, 2.09)	3.45	(0.94, 8.84)
		65 to 74	4.00	0.74	(0.20, 1.88)	2.59	(0.71, 6.64)
		≥75	0.00	0.00	(0.00, 1.40)	0.00	(0.00, 5.41)
	Male	18 to 29	15.00	1.11	(0.62, 1.83)	3.59	(2.01, 5.92)
		30 to 39	4.00	0.46	(0.13, 1.18)	1.50	(0.41, 3.85)
		40 to 49	5.00	0.94	(0.30, 2.18)	3.22	(1.05, 7.53)
		50 to 64	4.00	0.43	(0.12, 1.11)	1.59	(0.43, 4.06)
		65 to 74	1.00	0.24	(0.01, 1.32)	0.91	(0.02, 5.06)
EU	Female	18 to 29	4.00	2.14	(0.58, 5.49)	15.57	(4.24, 39.86)
		30 to 39	2.00	0.55	(0.07, 1.97)	2.44	(0.30, 8.81)
		40 to 49	7.00	1.73	(0.70, 3.57)	6.88	(2.77, 14.19)
		50 to 64	5.00	0.97	(0.31, 2.26)	4.08	(1.33, 9.53)
		65 to 74	2.00	0.44	(0.05, 1.60)	1.56	(0.19, 5.63)
	Male	18 to 29	31.00	2.15	(1.46, 3.04)	6.96	(4.73, 9.87)
		30 to 39	12.00	1.22	(0.63, 2.12)	3.98	(2.05, 6.95)
		40 to 49	5.00	0.79	(0.26, 1.85)	2.73	(0.89, 6.38)
		50 to 64	14.00	1.45	(0.79, 2.44)	5.31	(2.90, 8.90)
		65 to 74	2.00	0.59	(0.07, 2.14)	2.26	(0.27, 8.18)
		≥75	1.00	0.54	(0.01, 3.01)	2.23	(0.06, 12.40)

Key: CI=Confidence Interval; EOI=Event(s) of Interest; EU=European Union; LB=Lower Bound; O/E=Observed versus Expected; PE=Point Estimate; RP=Reporting Percentage; US=United States

a: Counts included EOI (from valid cases) that occurred within the risk window (Day: 1 to 42) only.

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

The US restricted sensitivity analysis showed an O/E ratio of >1 for all female and male age groups concerned except the female ≥75 age group and the male 65 to 74 age group. Of these, the O/E ratio was statistically significant above 1 (lower bound of 95% confidence interval >1) for the female 18 to 29, 30 to 39, and 40 to 49, and male 18 to 29 and 40 to 49 age groups only. The EU restricted sensitivity analysis showed an O/E ratio of >1 for all female and male age groups concerned. Of these, the O/E ratio was statistically significant above 1 (lower bound of 95% confidence interval >1) for the female 18 to 29, 40 to 49, and 50 to 64 age groups, and male 18 to 29, 30 to 39, and 50 to 64 age groups.

A restricted analysis, to include sensitivity analysis, was not performed for the EU 65 to 74 age group in the previous PBRER with DLP 24 February 2022. At the time of the current PBRER DLP, the EU 65 to 74 age group restricted sensitivity O/E ratio was >1. This O/E ratio was not statistically significant above 1 (lower bound of 95% confidence interval <1).

Pericarditis

Results of the restricted O/E and sensitivity analysis are presented in Table 113.

Table 113: Pericarditis: Restricted O/E and Sensitivity Analysis Results (Cumulative Through 24 August 2022)

Restricted 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	Female	30 to 39	8.00	0.36	(0.16, 0.72)	0.97	(0.42, 1.91)

Key: CI=Confidence Interval; EOI=Event(s) of Interest; EU=European Union; LB=Lower Bound; O/E=Observed versus Expected; PE=Point Estimate; RP=Reporting Percentage; US=United States

a: Counts included EOI (from valid cases) that occurred within the risk window (Day: 1 to 42) only.

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

The US restricted sensitivity analysis showed an O/E ratio of <1 for the female 30 to 39 age group.

Results of the US and EU O/E analysis (both broad and restricted, where applicable) are provided in Appendix 7.2, this includes cumulative exposure, expected counts and background incidence rates.

Conclusion

Based on the evaluation of the cases, and review of safety from other sources, the information is consistent with the information known about cardiac inflammatory disorders, including myocarditis and pericarditis. The Company will continue to closely monitor cardiac inflammatory disorders, including myocarditis and pericarditis, as an AESI.

16.3.6.1.2. Cardiomyopathy

Introduction

Cardiomyopathy is listed as an AESI in the cRMP, EU RMP, and the US PVP.

Methods

The Company global safety database was searched for medically confirmed and medically unconfirmed cases received during this reporting period and cumulatively, which coded to the search criteria provided in Appendix 5.

An O/E analysis has been performed and information is presented in the O/E analysis subsection below.

Results/Discussion

Primary Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 17 (12 medically confirmed and 5 medically unconfirmed) initial, primary dose cases reporting cardiomyopathy were identified. All 17 cases were serious and reported a total of 18 serious EOI.

Of these 17 primary dose cases received during the interval reporting period, 1 was reported from a Janssen Sponsored Clinical Study and 16 from post-marketing spontaneous sources. No cases were reported from Janssen Supported Clinical Studies.

Cumulatively, 74 (49 medically confirmed and 25 medically unconfirmed) primary dose cases reporting cardiomyopathy were identified. All 74 cases were serious and reported a total of 82 EOI (79 serious; 3 nonserious).

Of the 74 cumulative primary dose cases received, 4 were reported from Janssen Sponsored Clinical Studies and 70 from post-marketing spontaneous sources. No cases were reported from Janssen Supported Clinical Studies.

Janssen Sponsored Clinical Studies Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 1 initial, primary dose case reporting cardiomyopathy was retrieved from a Janssen Sponsored Clinical Study. This case was reported from VAC31518COV3009 and concerned a 45-year-old male from [redacted] who experienced a serious EOI of myocardial fibrosis. The TTO was reported as 90.0 days from the first dose, and the outcome was not resolved.

Janssen Supported Clinical Studies Primary Dose Cases

There were no initial, primary dose cases retrieved from the search of the Company global safety database during the reporting period of 25 February 2022 to 24 August 2022.

Post-marketing Sources (Including Spontaneous and Solicited) Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 16 post-marketing sources (including spontaneous and solicited), initial, primary dose cases reporting cardiomyopathy were retrieved. These 16 post-marketing, initial, primary dose cases reported 17 serious EOI.

Cumulatively, 70 (45 medically confirmed and 25 medically unconfirmed) post-marketing, primary dose cases reporting cardiomyopathy were identified. All 70 cases were serious and reported a total of 78 EOI (75 serious; 3 nonserious).

An overview of these cases is presented in Table 114 below.

Table 114: Characteristics of Post-marketing, Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Cardiomyopathy

Case Characteristics		Number of Cases Received During the Interval Reporting Period=16	Number of Cases Received Cumulatively=70
Sex	Male	14	50
	Female	2	18
	NR	0	2
Age (Years)[a]	18 to 35	2	10
Minimum: 19	36 to 50	4	18
Maximum: 70	51 to 64	7	26
Mean: 51.3	≥65	2	14
Median: 56.0	Elderly	1	1
	NR	0	1
Sources	Spontaneous	16	70
Country/Territory[b]	Germany	6	16
	United States	6	43
	France	1	3
	Italy	1	1
	Latvia	1	1
	Philippines	1	1
Event Characteristics		**Number of Events=17**	**Number of Events=78**
Seriousness (Event Level)[c]	Serious	17	75
	Nonserious	0	3
Outcome (Event Level)[c]	Not resolved	4	27
	Resolving	3	8
	Fatal	2	11
	Resolved	2	12
	Resolved with sequelae	2	3
	NR	4	17

Key: NR=Not Reported
a: The calculation was based on the current reporting period (25 February 2022 to 24 August 2022). Age group was presented for cases where age was not reported.
b: Countries/Territories were presented in decreasing order for the current reporting period (25 February 2022 to 24 August 2022).
c: Seriousness and outcome have been presented for the events of interest. A single case may report more than 1 event of interest.

Of these 16 post-marketing, initial, primary dose cases, the most frequently reported countries/territories of origin (n≥6) were Germany and the US (n=6 each). These cases concerned 14 males and 2 females. The age range was from 19 to 70 years.

The frequency distribution of the MedDRA PTs of interest reported in post-marketing, primary dose cases is presented in Table 115 below. A single case may contain more than 1 EOI.

Table 115: Frequency of MedDRA PTs of Interest in Post-marketing, Primary Dose Cases Reporting Cardiomyopathy With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Cardiomyopathy	5	0	21	0
Congestive cardiomyopathy	3	0	9	0
Ejection fraction decreased	3	0	20	2

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: The MedDRA PTs of interest with a frequency ≥3 have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event of interest.

The EOI (n≥3) included cardiomyopathy (n=5), and congestive cardiomyopathy and ejection fraction decreased (n=3 each). The mean and median TTO were 91.6 and 13.0 days, respectively. Where reported (n=13), the outcomes were not resolved (n=4), resolving (n=3), and fatal, resolved and resolved with sequelae (n=2 each).

Fatal Post-marketing Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 3 post-marketing, initial, primary dose fatal cases with 2 fatal EOI were retrieved. The fatal EOI was hypertrophic cardiomyopathy in both cases. One case reported a TTO outside of the risk window of 30 days and for 1 case the TTO was not reported.

The case occurring outside the risk window was medically unconfirmed. This case was received via the Regulatory Authority (EVHUMAN Vaccines, [redacted] and concerned a 70-year-old male who experienced hypertrophic cardiomyopathy, and pulmonary thromboembolism on Day 202 post-vaccination and died 10 days later due to these events. No further details were reported. It was unspecified if an autopsy was performed. The lack of available information (specifically medical history/concurrent conditions, cosuspect/concomitant medications, and laboratory and diagnostic test results) precludes a meaningful medical assessment.

The second case was medically confirmed and concerned a 69-year-old male with no past medical history or concomitant conditions. Nine days after receiving Ad26.COV2.S, the patient experienced cerebral venous thrombosis, MI, coronary thrombosis, cerebral venous sinus thrombosis, severe coronary sclerosis, anti-pf4 antibodies, and cardiac hypertrophy. An unspecified duration later, the patient died of AMI. The outcome of cardiac hypertrophy and other events was not reported. An autopsy was performed, and the findings included cerebral venous sinus thrombosis (CVST) with non-significant neuropathologic changes, coronary sclerosis, coronary thrombosis, cardiac hypertrophy, fresh MI and anti-PF4 antibodies. The myocardial

histology showed fresh myocardial ischaemia, while the cerebral tissue did not show any significant alteration.

The third case was medically unconfirmed and concerned a 19-year-old male who experienced hypertrophic cardiomyopathy within a month after receiving Ad26.COV2.S and died. The patient's family reported that autopsy results found hypertrophic cardiomyopathy as the cause of death while gene test results did not show hypertrophic cardiomyopathy as the cause. This case lacks essential information regarding the patient's medical history, concomitant medication, the clinical course of events, diagnostic and laboratory results precluding any meaningful medical assessment.

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

Booster Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 1 initial case reported as booster was identified. This case was medically unconfirmed, serious and reported 1 serious EOI. This case was heterologous and was reported from a post-marketing spontaneous source. No cases were reported from Janssen Sponsored Clinical Studies or Janssen Supported Clinical Studies.

Cumulatively, 4 (1 medically confirmed and 3 medically unconfirmed) cases reported as booster were identified. All 4 cases were serious and reported a total of 4 serious EOI. Of these cases, 3 were heterologous and 1 was homologous.

All 4 cumulative booster dose cases received were reported from post-marketing spontaneous sources. No cases were reported from Janssen Sponsored Clinical Studies or Janssen Supported Clinical Studies.

A cumulative booster dose CIOMS II LL is presented in Appendix 8.2.

Janssen Sponsored and Janssen Supported Clinical Studies (Booster Dose Cases)

There were no initial cases reported as booster which were retrieved from the search of the Company global safety database during the interval reporting period of 25 February 2022 to 24 August 2022 for either the Janssen Sponsored or Janssen Supported Clinical Studies.

Post-marketing Sources (Including Spontaneous and Solicited) Booster Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 1 initial case reported as booster was retrieved from a post-marketing spontaneous source. This case concerned a 50-year-old male from [redacted] who experienced a serious EOI of ejection fraction decreased. The TTO was 224 days from the first dose and the outcome was resolving.

Cumulatively, 4 (1 medically confirmed and 3 medically unconfirmed) post-marketing cases reported as booster were identified. All cases were serious and reported a total of 4 serious EOI.

Fatal Post-marketing Booster Dose Cases

There were no fatal cases reported as booster which were retrieved from the search of the Company global safety database during the interval reporting period of 25 February 2022 to 24 August 2022.

Literature ICSR

ICSR literature cases received during the reporting period of 25 February 2022 to 24 August 2022 were reviewed, and no information was identified that would change the characterisation of risk.

Discussion

The majority of the cases reported during the interval were reported from the US and Germany and were males (87.5%). The median age was 56 years. Overall, no specific patterns among cases reporting cardiomyopathy were identified.

O/E Analysis Results

Appendix 7.1 contains the methodology used to calculate and perform the O/E analyses for the AESI. Results of the restricted O/E and sensitivity analysis are presented in Table 116.

Table 116: Cardiomyopathies: Restricted O/E and Sensitivity Analysis Results (Cumulative Through 24 August 2022)

Restricted 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	14.00	3.13	(1.71, 5.26)	6.43	(3.52, 10.79)
	≥60	9.00	0.70	(0.32, 1.33)	2.36	(1.08, 4.48)
EU	18 to 59	7.00	1.37	(0.55, 2.82)	2.81	(1.13, 5.79)
	≥60	4.00	0.39	(0.11, 1.01)	1.33	(0.36, 3.41)

Key: CI=Confidence Interval; EOI=Event(s) of Interest; EU=European Union; LB=Lower Bound; O/E=Observed versus Expected; PE=Point Estimate; RP=Reporting Percentage; US=United States

a: Counts included EOI (from valid cases) with that occurred within the risk window (Day: 1 to 30) only.

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

The US restricted sensitivity analysis showed an O/E ratio of >1 for both age groups. The O/E ratio was statistically significant above 1 (lower bound of 95% confidence interval >1) for both age groups. The EU restricted sensitivity analysis showed a statistically significant O/E ratio of >1 (lower bound of 95% confidence interval <1) for the 18 to 59 age group. Since the previous PBRER DLP (24 February 2022), for the EU 18 to 59 and ≥60 age groups, the restricted sensitivity O/E ratio showed an increase from <1 to >1. The O/E ratio was statistically significant above 1 (lower bound of 95% confidence interval >1) in the EU for the 18 to 59 age group.

Results of the US and EU O/E analysis (both broad and restricted, where applicable) are provided in Appendix 7.2, this includes cumulative exposure, expected counts and background incidence rates.

Conclusion

Based on the evaluation of the cases, and review of safety from other sources, the information is consistent with the information known about cardiomyopathy. The Company will continue to closely monitor cardiomyopathy as an AESI.

16.3.6.1.3. Coronary Artery Disease, Including Acute Myocardial Infarction

Introduction

Coronary artery disease (CAD), including acute myocardial infarction (AMI) is listed as an AESI in the cRMP, EU RMP, and the US PVP.

Methods

The Company global safety database was searched for medically confirmed and medically unconfirmed cases received during this reporting period and cumulatively, which coded to the search criteria provided in Appendix 5.

An O/E analysis has been performed and information is presented in the O/E Analysis subsection below.

Results/Discussion

Primary Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 204 (114 medically confirmed and 90 medically unconfirmed) initial, primary dose cases reporting CAD, including acute MI were identified. Of these 204 cases, 203 were serious and 1 was nonserious and reported a total of 230 EOI (228 serious; 2 nonserious).

Of these 204 primary dose cases received during the interval reporting period, 62 were reported from Janssen Sponsored Clinical Studies and 142 from post-marketing sources (including spontaneous and solicited cases). No cases were reported from Janssen Supported Clinical Studies.

Cumulatively, 920 (544 medically confirmed and 376 medically unconfirmed) primary dose cases reporting CAD, including acute MI were identified. Of these cases, 914 were serious and 6 were nonserious and reported a total of 1,105 EOI (1,092 serious; 13 nonserious).

Of the 920 cumulative primary dose cases received, 192 were reported from Janssen Sponsored Clinical Studies, 3 from Janssen Supported Clinical Studies, and 725 from post-marketing sources (including spontaneous and solicited cases).

Janssen Sponsored Clinical Studies Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 62 initial, primary dose cases reporting CAD, including acute MI were retrieved from Janssen Sponsored Clinical Studies. Of the 62 cases, 32 were from VAC31518COV3001 and 30 from VAC31518COV3009. These 62 cases reported 62 serious EOI. Of these 62 cases, the most frequently reported countries/territories of origin (n≥10) were the US (n=22), followed by Brazil (n=10). These cases concerned 44 males and 18 females. The age range was from 33 to 90 years.

The EOI (n≥5) included acute myocardial infarction (n=14), coronary artery disease and myocardial infarction (n=11 each), and arteriosclerosis coronary artery (n=5). The mean and median TTO were 353.9 and 350.5 days, respectively. The outcomes were resolved (n=37), fatal and resolving (n=7 each), not resolved (n=6), and resolved with sequelae (n=5).

Janssen Supported Clinical Studies Primary Dose Cases

There were no initial, primary dose cases retrieved from the search of the Company global safety database during the reporting period of 25 February 2022 to 24 August 2022.

Post-marketing Sources (Including Spontaneous and Solicited) Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 142 post-marketing sources (including spontaneous and solicited), initial, primary dose cases reporting CAD, including acute MI were retrieved. These 142 initial, post-marketing, primary dose cases reported 168 EOI (166 serious; 2 nonserious).

Cumulatively, 725 (349 medically confirmed and 376 medically unconfirmed) post-marketing, primary dose cases reporting CAD, including acute MI were identified. Of these cases, 721 were serious and 4 were nonserious and reported a total of 903 EOI (892 serious; 11 nonserious).

An overview of these cases is presented in Table 117 below.

Table 117: Characteristics of Post-marketing, Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Coronary Artery Disease, Including Acute Myocardial Infarction

Case Characteristics		Number of Cases Received During the Interval Reporting Period=142	Number of Cases Received Cumulatively=725
Sex	Male	95	433
	Female	44	263
	NR	3	29
Age (Years)[a]	18 to 35	21	98
Minimum: 19	36 to 50	31	149
Maximum: 96	51 to 64	55	245
Mean: 53.4	≥65	29	181
	Adult	2	5

Table 117: Characteristics of Post-marketing, Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Coronary Artery Disease, Including Acute Myocardial Infarction

Case Characteristics		Number of Cases Received During the Interval Reporting Period=142	Number of Cases Received Cumulatively=725
Median: 54.5	Elderly	0	1
	NR	4	46
Sources	Spontaneous	135	706
	Clinical study (noninterventional; solicited)	5	16
	Interventional clinical trial	2	3
Country/Territory[b]	United States	44	413
	Germany	43	113
	Philippines	11	19
	Poland	11	17
	Austria	7	21
	Greece	6	8
Event Characteristics		**Number of Events=168**	**Number of Events=903**
Seriousness (Event Level)[c]	Serious	166	892
	Nonserious	2	11
Outcome (Event Level)[c]	Not resolved	46	249
	Resolved	30	171
	Fatal	24	130
	Resolving	21	90
	Resolved with sequelae	10	38
	NR	37	225

Key: NR=Not Reported

a: The calculation was based on the current reporting period (25 February 2022 to 24 August 2022). Age group was presented for cases where age was not reported.

b: Countries/Territories with frequency ≥6 were presented in decreasing order for the current reporting period (25 February 2022 to 24 August 2022).

c: Seriousness and outcome have been presented for the events of interest. A single case may report more than 1 event of interest.

Of these 142 post-marketing, initial, primary dose cases, the most frequently reported countries/territories of origin (n≥43) were the US (n=44), followed by Germany (n=43). These cases concerned 95 males, 44 females, and 3 did not report sex. The age range was from 19 to 96 years.

The frequency distribution of the MedDRA PTs of interest reported in post-marketing, primary dose cases is presented in Table 118 below. A single case may contain more than 1 EOI.

Table 118: Frequency of MedDRA PTs of Interest in Post-Marketing, Primary Dose Cases Reporting Coronary Artery Disease, Including Acute Myocardial Infarction With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Angina pectoris	63	0	185	0
Myocardial infarction	38	0	272	0
Acute myocardial infarction	21	0	137	0

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: The MedDRA PTs of interest with a frequency ≥20 have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event of interest.

The EOI (n>20) included angina pectoris (n=63), myocardial infarction (n=38), and acute myocardial infarction (n=21). The mean and median TTO were 81.6 and 14.0 days, respectively. Where reported (n=131), the outcomes were not resolved (n=46), resolved (n=30), fatal (n=24), resolving (n=21), and resolved with sequelae (n=10).

Fatal Post-marketing Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 18 post-marketing, initial, primary dose fatal cases with 26 fatal EOI were retrieved (see Appendix 8.3.1). The fatal EOI were myocardial infarction (n=12), acute myocardial infarction (n=6), troponin increased, coronary artery thrombosis (n=2 each), and arteriosclerosis coronary artery, coronary arterial stent insertion, myocardial ischaemia, and percutaneous coronary intervention (n=1 each).

Four fatal cases reported a TTO within the risk window of 28 days. All 4 cases are medically confirmed. Patient age ranged from 38 to 96 years, and TTO was reported in 3 cases and ranged from 4 to 16 days post-vaccination. The cause of death was reported due to MI (n=2), MI and coronary artery thrombosis (n=1), acute kidney injury, acute MI, anaemia of chronic disease, aspiration, atrial fibrillation, azotaemia, condition aggravated, confusional state, delirium, disease progression, encephalopathy, end-stage renal disease, general physical health deterioration, hyperkalaemia, hypernatraemia, metabolic acidosis, metabolic encephalopathy, multimorbidity, myocardial ischaemia, pneumonia aspiration, rhabdomyolysis, superficial vein thrombosis, and troponin increased (n=1). Of these 4 cases, 3 contained evidence of an alternative aetiology/identified risk factor for the development of an EOI. This included concurrent conditions of coronary sclerosis (n=1), hypertension (n=1), and chronic kidney disease (n=1).

The remaining case was reported in a 38-year-old female who experienced an MI on an unspecified date post-vaccination. This case lacked essential information (medical history/concurrent conditions, latency, autopsy report, clinical course details including diagnostic/laboratory workup, and concomitant medications) precluding any meaningful medical assessment.

Fourteen cases reported TTO outside of the risk window of 28 days. Twelve cases were medically confirmed, and 2 were medically unconfirmed. Patient age ranged from 29 to 94 years and the

TTO ranged from 35 to 310 days post-vaccination. The cause of death was reported due to MI (n=7), unspecified cause (n=4), AMI, Sepsis and COVID-19 pneumonia (n=1), MI, hypertension, and hypertensive heart disease (n=1), and MI and COVID-19 infection (n=1). The majority of the cases (13/14, 93%) reported an alternative aetiology/identified risk factor for the development of an EOI. This included underlying cardiac history (n=6), concurrent COVID-19 infection (n=5), sepsis (n=1), and obstructive sleep apnoea, and hyperlipidaemia (n=1). The remaining case lacked essential information (medical history/concurrent conditions, autopsy report, clinical course details including diagnostic/laboratory workup, and concomitant medications) precluding any meaningful medical assessment.

Of these 14 cases, 1 reported the age of the patient as < 40 years. A summary of the case is shown below:

A 29-year-old male who was reported as healthy with no current illnesses or known allergies, experienced sepsis, MI, and organ failure 131 days post-vaccination. Five days later, the patient died from an unknown cause. It was not reported whether an autopsy was performed.

Booster Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 27 (7 medically confirmed and 20 medically unconfirmed) initial cases reported as booster were identified. All 27 cases were serious and reported a total of 29 serious EOI. Of these cases, 16 were heterologous and 11 were homologous.

Of these 27 cases reported as booster during the interval, 1 was reported from a Janssen Sponsored Clinical Study and 26 from post-marketing spontaneous sources. No cases were reported from Janssen Supported Clinical Studies.

Cumulatively, 44 (15 medically confirmed and 29 medically unconfirmed) cases reported as booster were identified. All 44 cases were serious and reported a total of 50 serious EOI. Of these cases, 25 were heterologous and 19 were homologous.

Of the 44 cumulative booster dose cases received, 1 was reported from a Janssen Sponsored Clinical Study, 1 from a Janssen Supported Clinical Study, and 42 from post-marketing spontaneous sources.

A cumulative booster dose CIOMS II LL is presented in Appendix 8.3.2.

Janssen Sponsored Clinical Studies Booster Dose Cases

During the interval reporting period of 25 February 2022 to 24 August 2022, 1 initial case reported as booster was retrieved from a Janssen Sponsored Clinical Study. This case was reported from VAC31518COV3001 and concerned a 56-year-old male from [redacted] who experienced a serious EOI of acute coronary syndrome. The TTO was reported as 120 days from the first dose and the outcome was reported as resolving.

Janssen Supported Clinical Studies Booster Dose Cases

There were no initial cases reported as booster which were retrieved from the search of the Company global safety database during the interval reporting period of 25 February 2022 to 24 August 2022.

Post-marketing Sources (Including Spontaneous and Solicited) Booster Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 26 post-marketing sources (including spontaneous and solicited), initial cases reported as booster were retrieved. These 26 post-marketing, booster dose cases reported 28 serious EOI.

Cumulatively, 42 (13 medically confirmed and 29 medically unconfirmed) post-marketing cases reported as booster were identified. All 42 cases were serious and reported a total of 48 serious EOI.

An overview of these cases is presented in Table 119 below.

Table 119: Characteristics of Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Coronary Artery Disease, Including Acute Myocardial Infarction

Case Characteristics		Number of Cases Received During the Interval Reporting Period=26	Number of Cases Received Cumulatively=42
Sex	Male	17	26
	Female	9	13
	NR	0	3
Age (Years)[a] **Minimum: 13** **Maximum: 84** **Mean: 51.2** **Median: 51.5**	<18	1	1
	18 to 35	2	3
	36 to 50	7	8
	51 to 64	8	13
	≥65	4	8
	Adult	1	2
	NR	3	7
Country/Territory[b]	Austria	7	7
	Germany	7	7
	United States	7	18
	Brazil	2	3
Sources	Spontaneous	26	42
Classification	Heterologous	16	25
	Homologous	10	17
Event Characteristics		**Number of Events=28**	**Number of Events=48**
Seriousness (Event Level)[c]	Serious	28	48
Outcome (Event Level)[c]	Not resolved	9	11
	Resolved	8	10
	Fatal	4	9

Table 119: Characteristics of Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Coronary Artery Disease, Including Acute Myocardial Infarction

Case Characteristics		Number of Cases Received During the Interval Reporting Period=26	Number of Cases Received Cumulatively=42
	Resolving	3	4
	NR	4	14

Key: NR=Not Reported
a: The calculation was based on the current reporting period (25 February 2022 to 24 August 2022). Age group was presented for cases where age was not reported.
b: Countries/Territories with a frequency ≥2 were presented in decreasing order for the current reporting period (25 February 2022 to 24 August 2022).
c: Seriousness and outcome have been presented for the events of interest. A single case may report more than 1 event of interest.

Of these 26 post-marketing, initial cases reported as booster, the most frequently reported countries/territories of origin (n≥2) were Austria, Germany, and the US (n=7 each), followed by Brazil (n=2). These cases concerned 17 males and 9 females. The age range was from 13 to 84 years.

The frequency distribution of the MedDRA PTs of interest reported in post-marketing cases reported as booster is presented in Table 120 below. A single case may contain more than 1 EOI.

Table 120: Frequency of MedDRA PTs of Interest in Post-marketing Cases Reported as Booster Dose With the Use of Ad26.COV2.S and Reporting Coronary Artery Disease, Including Acute Myocardial Infarction

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Angina pectoris	14	0	16	0
Myocardial infarction	6	0	15	0

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: The MedDRA PTs of interest with a frequency ≥6 have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event of interest.

The EOI (n≥6) included angina pectoris (n=14) and myocardial infarction (n=6). The mean and median TTO were 90.8 and 42.5 days, respectively. Where reported (n=24), the outcomes were not resolved (n=9), resolved (n=8), fatal (n=4), and resolving (n=3).

Fatal Post-marketing Booster Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 5 initial, fatal cases reported as booster with 5 fatal EOI were retrieved. The fatal EOI were myocardial infarction (n=4) and acute myocardial infarction (n=1).

Homologous Booster Dose

One case reported a fatal EOI following a booster with Ad26.COV2.S. This case is medically unconfirmed and concerned a 55-year-old male who received 3 doses of Ad26.COV2.S. It was unknown whether the patient had experienced AEs following vaccination with the first 2 doses of Ad26.COV2.S. Two weeks after the third dose, the patient experienced what was described as a massive heart attack. On an unspecified date post-vaccination, the patient died from an unknown cause. It was unknown if an autopsy was performed. This case lacked essential information (medical history/concurrent conditions, clinical course details including diagnostic/laboratory workup, concomitant medications, and autopsy results) precluding any meaningful medical assessment.

Heterologous Booster Dose

Four cases involved a heterologous booster, where Ad26.COV2.S vaccine was reported as the primary dose and the booster dose was an mRNA vaccine. The EOI was reported in relation to the mRNA booster. The cause of death in these 4 cases was MI and thrombosis (n=2), MI (n=1), and AMI (n=1).

Literature ICSR

ICSR literature cases received during the reporting period of 25 February 2022 to 24 August 2022 were reviewed, and no information was identified that would change the characterisation of risk.

O/E Analysis Results

Appendix 7.1 contains the methodology used to calculate and perform the O/E analyses for the AESI.

Since the previous PBRER data lock point (24 February 2022), the broad O/E ratio has remained <1 in the US and EU for both age groups. A restricted O/E analysis with sensitivity analysis was not required.

Results of the US and EU O/E analysis (both broad and restricted, where applicable) are provided in Appendix 7.2, this includes cumulative exposure, expected counts and background incidence rates.

Conclusion

Based on the evaluation of the cases, and review of safety from other sources, the information is consistent with the information known about coronary artery disease, including acute myocardial infarction. The Company will continue to closely monitor coronary artery disease, including acute myocardial infarction as an AESI.

16.3.6.2. Musculoskeletal Disorders

16.3.6.2.1. Acute Aseptic Arthritis

Introduction

Acute aseptic arthritis is listed as an AESI in the cRMP, EU RMP, and the US PVP.

Methods

The Company global safety database was searched for medically confirmed and medically unconfirmed cases received during this reporting period and cumulatively, which coded to the search criteria provided in Appendix 5.

An O/E Analysis has been performed and information is presented in the O/E Analysis subsection below.

Results/Discussion

Primary Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 143 (66 medically confirmed and 77 medically unconfirmed) initial, primary dose cases reporting acute aseptic arthritis were identified. Of these 143 cases, 110 were serious and 33 were nonserious and reported a total of 153 EOI (109 serious; 44 nonserious).

Of these 143 primary dose cases received during the interval reporting period, 41 were reported from Janssen Sponsored Clinical Studies and 102 from post-marketing sources (including spontaneous and solicited cases). No cases were reported from Janssen Supported Clinical Studies.

Cumulatively, 610 (356 medically confirmed and 254 medically unconfirmed) primary dose cases reporting acute aseptic arthritis were identified. Of these cases, 349 were serious and 261 were nonserious and reported a total of 637 EOI (328 serious; 309 nonserious).

Of the 610 cumulative primary dose cases received, 100 were reported from Janssen Sponsored Clinical Studies, 2 from Janssen Supported Clinical Studies, and 508 from post-marketing sources (including spontaneous and solicited cases).

Janssen Sponsored Clinical Studies Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 41 initial, primary dose cases reporting acute aseptic arthritis were retrieved from Janssen Sponsored Clinical Studies. Of the 41 cases, 22 were from VAC31518COV3009, 17 from VAC31518COV3001, and 1 each from VAC31518COV2008 and VAC31518COV3005. These 41 cases reported 43 EOI (42 serious; 1 nonserious). Of these 41 cases, the most frequently reported countries/territories of origin ($n \geq 12$) were the US (n=17), followed by Belgium (n=12). These cases concerned 22 females and 19 males. The age range was from 20 to 82 years.

The EOI (≥2) included osteoarthritis (n=35) and spinal osteoarthritis and temporomandibular joint syndrome (n=2 each). The mean and median TTO were 333.4 and 353.0 days, respectively. Where reported (n=42), the outcomes were resolved (n=29), resolving (n=6), resolved with sequelae (n=4), not resolved (n=2), and fatal (n=1).

Janssen Supported Clinical Studies Primary Dose Cases

There were no initial, primary dose cases retrieved from the search of the Company global safety database during the reporting period of 25 February 2022 to 24 August 2022.

Post-marketing Sources (Including Spontaneous and Solicited) Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 102 post-marketing sources (including spontaneous and solicited), initial, primary dose cases reporting acute aseptic arthritis were retrieved. These 102 post-marketing, initial, primary dose cases reported 110 EOI (67 serious; 43 nonserious).

Cumulatively, 508 (254 medically confirmed and 254 medically unconfirmed) post-marketing, primary dose cases reporting acute aseptic arthritis were identified. Of these cases, 249 cases were serious and 259 were nonserious and reported a total of 533 EOI (227 serious; 306 nonserious).

An overview of these cases is presented in Table 121 below.

Table 121: Characteristics of Post-marketing, Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Acute Aseptic Arthritis

Case Characteristics		Number of Cases Received During the Interval Reporting Period=102	Number of Cases Received Cumulatively=508
Sex	Female	62	269
	Male	37	217
	NR	3	22
Age (Years)[a]	<18	1	1
Minimum: 14	18 to 35	14	46
Maximum: 77	36 to 50	36	199
Mean: 48.8	51 to 64	31	141
Median: 49.0	≥65	10	75
	Adult	5	12
	Elderly	0	2
	NR	5	32
Sources	Spontaneous	100	495
	Clinical study (noninterventional; solicited)	2	10
	Clinical study (noninterventional; unsolicited)	0	3
	United States	39	197

Table 121: Characteristics of Post-marketing, Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Acute Aseptic Arthritis

Case Characteristics		Number of Cases Received During the Interval Reporting Period=102	Number of Cases Received Cumulatively=508
Country/Territory[b]	Germany	32	62
	South Africa	8	11
	France	4	22
	Greece	4	6
	Austria	3	5
	Philippines	3	4
Event Characteristics		**Number of Events=110**	**Number of Events=533**
Seriousness (Event Level)[c]	Serious	67	227
	Nonserious	43	306
Outcome (Event Level)[c]	Not resolved	65	215
	Resolved	11	63
	Resolving	11	54
	Resolved with sequelae	6	9
	Fatal	2	4
	NR	15	188

Key: NR=Not Reported
a: The calculation was based on the current reporting period (25 February 2022 to 24 August 2022). Age group was presented for cases where age was not reported.
b: Countries/Territories with frequency ≥3 were presented in decreasing order for the current reporting period (25 February 2022 to 24 August 2022).
c: Seriousness and outcome have been presented for the events of interest. A single case may report more than 1 event of interest.

Of these 102 post-marketing, initial, primary dose cases, the most frequently reported countries/territories of origin (n≥32) were the US (n=39), followed by Germany (n=32). These cases concerned 62 females, 37 males, and 3 did not report sex. The age range was from 14 to 77 years.

The frequency distribution of the MedDRA PTs of interest reported in post-marketing, primary dose cases is presented in Table 122 below. A single case may contain more than 1 EOI.

Table 122: Frequency of MedDRA PTs of Interest in Post-marketing, Primary Dose Cases Reporting Acute Aseptic Arthritis With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Arthritis	9	19	33	225
Rheumatoid arthritis	28	0	92	0
Periarthritis	4	7	14	17
Rheumatic disorder	1	7	2	16
Osteoarthritis	2	4	9	14
Polyarthritis	5	0	17	0

Table 122: Frequency of MedDRA PTs of Interest in Post-marketing, Primary Dose Cases Reporting Acute Aseptic Arthritis With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: The MedDRA PTs of interest with a frequency ≥5 have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event of interest.

The EOI (≥5) included arthritis and rheumatoid arthritis (n=28 each), periarthritis (n=11), rheumatic disorder (n=8), osteoarthritis (n=6), and polyarthritis (n=5). The mean and median TTO were 28.8 and 8.0 days, respectively. Where reported (n=95), the outcomes were not resolved (n=65), resolved and resolving (n=11 each), resolved with sequelae (n=6), and fatal (n=2).

From the 102 post-marketing, initial, primary dose cases, 2 concerned a 59-year-old male and a 46-year-old female, who experienced rheumatoid arthritis 1 and 13 days post-vaccination with Ad26.COV2.S respectively. There were no identified risk factors/confounders that could have led to the EOI. Considering the plausible temporal relation and an absence of alternate aetiologies, causality with the vaccine cannot be excluded in these 2 cases.

Fatal Post-marketing Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 2 post-marketing, primary dose fatal cases with 2 fatal EOI were retrieved. The fatal EOI were gout and gouty tophus. The first case concerned a 48-year-old male, where the fatal event of gout occurred 303 days post-vaccination. The case provided limited information on clinical course, diagnostic workup, date of death, and autopsy details which precludes a meaningful medical assessment. The second case reporting fatal gouty tophus 26 days post-vaccination concerned a 46-year-old male with concurrent events of colorectal cancer, ileus secondary to ileocecal tuberculosis and hospital acquired pneumonia with subsequent septic shock, which could provide an alternate explanation to the fatal outcome. It was unknown if autopsy was performed in either case.

Booster Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 28 (6 medically confirmed and 22 medically unconfirmed) initial cases reported as booster were identified. There were 16 serious and 12 nonserious cases and reported a total of 31 EOI (13 serious; 18 nonserious). Of these cases, 19 were heterologous and 9 were homologous.

Of these 28 cases reported as booster during the interval, all were reported from post-marketing sources (including spontaneous and solicited). No cases were reported from Janssen Sponsored Clinical Studies or Janssen Supported Clinical Studies.

Cumulatively, 35 (8 medically confirmed and 27 medically unconfirmed) cases reported as booster were identified. Of these cases, 19 were serious and 16 were nonserious and reported a

total of 38 EOI (16 serious; 22 nonserious). Of these cases, 19 were heterologous and 16 were homologous.

Of the 35 cumulative booster dose cases received, all were reported from post-marketing sources (including spontaneous and solicited). No cases were reported from Janssen Sponsored Clinical Studies or Janssen Supported Clinical Studies.

A cumulative booster dose CIOMS II LL is presented in Appendix 8.4.

Janssen Sponsored and Janssen Supported Clinical Studies (Booster Dose Cases)

There were no initial cases reported as booster which were retrieved from the search of the Company global safety database during the interval reporting period of 25 February 2022 to 24 August 2022 for either the Janssen Sponsored or Janssen Supported Clinical Studies.

Post-marketing Sources (Including Spontaneous and Solicited) Booster Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 28 post-marketing sources (including spontaneous and solicited), initial cases reported as booster were retrieved. These 28 post-marketing, initial, booster dose cases reported 31 EOI (13 serious; 18 nonserious).

Cumulatively, 35 (8 medically confirmed and 27 medically unconfirmed) post-marketing cases reported as booster were identified. Of these cases, 19 were serious and 16 were nonserious and reported a total of 38 EOI (16 serious; 22 nonserious).

An overview of these cases is presented in Table 123 below.

Table 123: Characteristics of Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Acute Aseptic Arthritis

Case Characteristics		Number of Cases Received During the Interval Reporting Period=28	Number of Cases Received Cumulatively=35
Sex	Male	15	17
	Female	12	16
	NR	1	2
Age (Years)[a]	18 to 35	2	3
Minimum: 34	36 to 50	10	11
Maximum: 80	51 to 64	8	13
Mean: 53.6	≥65	6	6
Median: 53.0	Adult	1	1
	NR	1	1
Country/Territory[b]	Germany	10	10
	United States	9	14
	Brazil	3	3
	Philippines	2	2
Sources	Spontaneous	26	33

Table 123: Characteristics of Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Acute Aseptic Arthritis

Case Characteristics		Number of Cases Received During the Interval Reporting Period=28	Number of Cases Received Cumulatively=35
	Clinical study (noninterventional; unsolicited)	2	2
Classification	Heterologous	19	19
	Homologous	9	16
Event Characteristics		**Number of Events=31**	**Number of Events=38**
Seriousness (Event Level)[c]	Nonserious	18	22
	Serious	13	16
Outcome (Event Level)[c]	Not resolved	16	20
	Resolved with sequelae	3	3
	Resolved	2	2
	Resolving	2	2
	Fatal	1	1
	NR	7	10

Key: NR=Not Reported
a: The calculation was based on the current reporting period (25 February 2022 to 24 August 2022). Age group was presented for cases where age was not reported.
b: Countries/Territories with frequency ≥2 were presented in decreasing order for the current reporting period (25 February 2022 to 24 August 2022).
c: Seriousness and outcome have been presented for the events of interest. A single case may report more than 1 event of interest.

Of these 24 post-marketing, initial cases reported as booster, the most frequently reported countries/territories of origin (n≥9) were Germany (n=10), followed by the US (n=9). These cases concerned 15 males, 12 females, and 1 did not report sex. The age range was from 34 to 80 years.

The frequency distribution of the MedDRA PTs of interest reported in post-marketing cases reported as booster is presented in Table 124 below. A single case may contain more than 1 EOI.

Table 124: Frequency of MedDRA PTs of Interest in Post-marketing Cases Reported as Booster Dose With the Use of Ad26.COV2.S and Reporting Acute Aseptic Arthritis

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Arthritis	2	12	2	16
Rheumatoid arthritis	6	0	8	0
Osteoarthritis	2	1	2	1
Gout	1	1	1	1
Rheumatic disorder	0	2	0	2

Table 124: Frequency of MedDRA PTs of Interest in Post-marketing Cases Reported as Booster Dose With the Use of Ad26.COV2.S and Reporting Acute Aseptic Arthritis

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: The MedDRA PTs of interest with a frequency ≥2 have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022).

The EOI (≥2) included arthritis (n=14), rheumatoid arthritis (n=6), osteoarthritis (n=3), and gout and rheumatic disorder (n=2 each). The mean and median TTO were 127.5 and 166.0 days, respectively. Where reported (n=24), the outcomes were not resolved (n=16), resolved with sequelae (n=3), resolved and resolving (n=2 each), and fatal (n=1).

Fatal Post-marketing Booster Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 1 fatal case reported as booster with 1 fatal EOI was retrieved. The fatal EOI was arthritis. The case concerned a 74-year-old male with a medical history significant for a mild stroke and concurrent hypertension, who experienced the EOI 301 days post primary dose with Ad26.COV2.S, 155 days post booster dose with elasomeran (Dose 2) and 1 day post booster dose with tozinameran (Dose 3). The case was missing information on clinical course leading up the patient's death, diagnostic workup, and autopsy details, which precludes a meaningful medical assessment. It was unknown if autopsy was performed.

Literature ICSR

No ICSR literature cases were received during the reporting period of 25 February 2022 to 24 August 2022.

O/E Analysis Results

Appendix 7.1 contains the methodology used to calculate and perform the O/E analyses for the AESI.

Since the previous PBRER DLP (24 February 2022), the broad O/E ratio has remained <1 in the US and EU for both age groups. A restricted O/E analysis with sensitivity analysis was not required.

Results of the US and EU O/E analysis (both broad and restricted, where applicable) are provided in Appendix 7.2, this includes cumulative exposure, expected counts and background incidence rates.

Conclusion

Based on the evaluation of the cases, and review of safety from other sources, the information is consistent with the information known about acute aseptic arthritis. The Company will continue to closely monitor acute aseptic arthritis as an AESI.

16.3.6.3. Nervous System Disorders

16.3.6.3.1. Generalised Convulsion

Introduction

Generalised convulsion is listed as an AESI in the cRMP, EU RMP, and the US PVP.

Methods

The Company global safety database was searched for medically confirmed and medically unconfirmed cases received during this reporting period and cumulatively, which coded to the search criteria provided in Appendix 5.

An O/E analysis has been performed and information is presented in the O/E Analysis subsection below.

Results/Discussion

Primary Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 168 (106 medically confirmed and 62 medically unconfirmed) initial, primary dose cases reporting generalised convulsion were identified. Of these 168 cases, 153 were serious and 15 were nonserious and reported a total of 169 EOI (154 serious; 15 nonserious).

Of these 168 initial, primary dose cases received during the interval reporting period, 10 were reported from Janssen Sponsored Clinical Studies and 158 from post-marketing sources (including spontaneous and solicited cases). No cases were reported from Janssen Supported Clinical Studies.

Cumulatively, 559 (303 medically confirmed and 256 medically unconfirmed) primary dose cases reporting generalised convulsion were identified. Of these cases, 537 cases were serious and 22 were nonserious and reported a total of 578 EOI (551 serious; 27 nonserious).

Of the 559 cumulative primary dose cases received, 17 were reported from Janssen Sponsored Clinical Studies, 7 from Janssen Supported Clinical Studies, and 535 from post-marketing sources (including spontaneous and solicited cases).

Janssen Sponsored Clinical Studies Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 10 initial, primary dose cases reporting generalised convulsion were retrieved from Janssen Sponsored Clinical Studies. Of the 10 cases, 6 were from VAC31518COV3001 and 2 each from VAC31518COV3009 and

VAC31518COV2008. These 10 cases reported 10 serious EOI. Of these 10 cases, the most frequently reported countries/territories of origin were South Africa (n=5), followed by the US (n=4). These cases concerned 6 females and 4 males. The age range was from 35 to 80 years.

The EOI included seizure (n=6) and epilepsy, generalised tonic-clonic seizure, hyperglycaemic seizure, and partial seizures (n=1 each). The mean and median TTO were 351.8 and 403.0 days, respectively. The outcomes were reported as resolved (n=6) and fatal, not resolved, resolved with sequelae, and resolving (n=1 each).

Janssen Supported Clinical Studies Primary Dose Cases

There were no initial, primary dose cases retrieved from the search of the Company global safety database during the reporting period of 25 February 2022 to 24 August 2022.

Post-marketing Sources (Including Spontaneous and Solicited) Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 158 post-marketing sources (including spontaneous and solicited), initial, primary dose cases reporting generalised convulsion were retrieved. These 158 post-marketing, initial, primary dose cases reported 159 EOI (144 serious; 15 nonserious).

Cumulatively, 535 (279 medically confirmed and 256 medically unconfirmed) post-marketing, primary dose cases reporting generalised convulsion were identified. Of these cases, 514 were serious and 21 were nonserious and reported a total of 554 EOI (528 serious; 26 nonserious).

An overview of these cases is presented in Table 125 below.

Table 125: Characteristics of Post-marketing, Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Generalised Convulsion

Case Characteristics		Number of Cases Received During the Interval Reporting Period=158	Number of Cases Received Cumulatively=535
Sex	Male	52	260
	Female	45	190
	NR	61	85
Age (Years)[a]	<18	1	2
Minimum: 16	18 to 35	92	258
Maximum: 79	36 to 50	45	129
Mean: 35.3	51 to 64	14	60
Median: 33.0	≥65	4	31
	Adult	0	5
	Elderly	0	1
	Neonate	0	1
	NR	2	48
Sources	Spontaneous	157	530
	Clinical study (noninterventional; solicited)	1	5
	Poland	99	118

Table 125: Characteristics of Post-marketing, Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Generalised Convulsion

Case Characteristics		Number of Cases Received During the Interval Reporting Period=158	Number of Cases Received Cumulatively=535
Country/Territory[b]	South Africa	15	17
	Germany	11	42
	Cote d'Ivoire	8	8
	United States	7	167
	Portugal	4	25
	Kenya	3	3
	Philippines	3	17
Event Characteristics		**Number of Events=159**	**Number of Events=554**
Seriousness (Event Level)[c]	Serious	144	528
	Nonserious	15	26
Outcome (Event Level)[c]	Resolved	43	191
	Resolving	34	63
	Not resolved	18	70
	Resolved with sequelae	4	15
	Fatal	1	16
	NR	59	199

Key: NR=Not Reported

a: The calculation was based on the current reporting period (25 February 2022 to 24 August 2022). Age group was presented for cases where age was not reported.

b: Countries/Territories with frequency ≥3 were presented in decreasing order for the current reporting period (25 February 2022 to 24 August 2022).

c: Seriousness and outcome have been presented for the events of interest. A single case may report more than 1 event of interest.

Of these 158 post-marketing, initial, primary dose cases, the most frequently reported countries/territories of origin (n≥11) were Poland (n=99), followed by South Africa (n=15), and Germany (n=11). These cases concerned 52 males, 45 females, and 61 did not report sex. The age range was from 16 to 79 years.

The frequency distribution of the MedDRA PTs of interest reported in post-marketing, primary dose cases is presented in Table 126 below. A single case may contain more than 1 EOI.

Table 126: Frequency of MedDRA PTs of Interest in Post-marketing, Primary Dose Cases Reporting Generalised Convulsion With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Seizure	122	0	391	0
Febrile convulsion	6	15	11	20
Epilepsy	8	0	42	0
Generalised tonic-clonic seizure	4	0	38	0

Table 126: Frequency of MedDRA PTs of Interest in Post-marketing, Primary Dose Cases Reporting Generalised Convulsion With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: The MedDRA PTs of interest with a frequency ≥4 have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event of interest.

The EOI (≥4) included seizure (n=122), febrile convulsion (n=21), epilepsy (n=8), and generalised tonic-clonic seizure (n=4). The mean and median TTO were 10.9 and 0 days, respectively. Where reported (n=100), the outcomes were resolved (n=43), resolving (n=34), not resolved (n=18), resolved with sequelae (n=4), and fatal (n=1).

Fatal Post-marketing Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 2 post-marketing, initial, primary dose fatal cases, each reporting 1 fatal EOI, were retrieved. The fatal EOI were epilepsy in 1 case and seizure in the other. Both cases were medically confirmed.

One case was reported from a clinical trial (VAC3118COV3009) and concerned a 37-year-old female with a medical history of epilepsy and morbid obesity (Body Mass Index 41.6). Concomitant medications included ethinylestradiol/levonorgestrel for contraception. On Day 426 after primary vaccination with Ad26.COV2.S and Day 376 after booster dose of Ad26.COV2.S, the patient experienced epilepsy and died. No autopsy was performed and the death certificate was not provided. The Investigator's causality assessment for the EOI and Ad26.COV2.S was reported as not related. TTO of the EOI was well beyond the risk window for convulsions/seizures. History of loss of consciousness at the time of the EOI, and tonic, clonic, tonic-clonic or atonic motor manifestations were not reported. This case lacked essential details (treatment of the patient's underlying epilepsy, clinical course and treatment of the EOI, or laboratory results and diagnostic testing), which precluded a meaningful medical assessment. Additionally, the patient's underlying epilepsy provide an alternative aetiology for the EOI, and obesity and hormonal contraception may have been contributory factors.

The other case concerned a 24-year-old male who experienced generalised weakness, loss of consciousness, and seizure on Day 1 after vaccination and died 2 days later. Although loss of consciousness at the time of the EOI was reported, it was not reported if the patient had a history of loss of consciousness or experienced tonic, clonic, tonic-clonic or atonic motor manifestations at the time of the EOI. Essential details (medical history/concurrent conditions, concomitant medications, clinical course for EOI, treatment, laboratory results, diagnostic testing) were not reported, which precluded a meaningful medical assessment. It was not known if an autopsy was performed.

Booster Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 11 (2 medically confirmed and 9 medically unconfirmed) initial cases reported as booster were identified. All 11 cases were serious and reported a total of 12 serious EOI. Of these cases, 6 were homologous and 5 were heterologous.

Of these 11 cases reported as booster during the interval, all were from post-marketing sources (including spontaneous and solicited). No cases were reported from Janssen Sponsored Clinical Studies or Janssen Supported Clinical Studies.

Cumulatively, 16 (7 medically confirmed and 9 medically unconfirmed) cases reported as booster were identified. All 16 cases were serious and reported a total of 17 serious EOI. Of these cases, 9 were homologous and 7 were heterologous.

Of the 16 cumulative booster dose cases received, 1 was reported from a Janssen Supported Clinical Study and 15 from post-marketing sources (including spontaneous and solicited cases). No cases were reported from Janssen Sponsored Clinical Studies.

A cumulative booster dose CIOMS II LL is presented in Appendix 8.5.

Janssen Sponsored and Janssen Supported Clinical Studies (Booster Dose Cases)

There were no initial cases reported as booster which were retrieved from the search of the Company global safety database during the interval reporting period of 25 February 2022 to 24 August 2022 for either the Janssen Sponsored or Janssen Supported Clinical Studies.

Post-marketing Sources (Including Spontaneous and Solicited) Booster Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 11 post-marketing sources (including spontaneous and solicited), initial cases reported as booster were retrieved. These 11 post-marketing, initial booster dose cases reported 12 serious EOI.

Cumulatively 15 (6 medically confirmed and 9 medically unconfirmed) post-marketing cases reported as booster were identified. All 15 cases were serious and reported a total of 16 serious EOI.

An overview of these cases is presented in Table 127 below.

Table 127: Characteristics of Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Generalised Convulsion

Case Characteristics		Number of Cases Received During the Interval Reporting Period=11	Number of Cases Received Cumulatively=15
Sex	Female	7	10
	Male	3	4

Table 127: Characteristics of Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Generalised Convulsion

Case Characteristics		Number of Cases Received During the Interval Reporting Period=11	Number of Cases Received Cumulatively=15
	NR	1	1
Age (Years)[a] **Minimum: 20** **Maximum: 56** **Mean: 39.8** **Median: 36.5**	18 to 35 36 to 50 51 to 64 NR	5 1 4 1	6 1 7 1
Country/Territory[b]	Germany Brazil United States South Africa	4 3 3 1	4 3 5 1
Sources	Spontaneous	11	15
Classification	Homologous Heterologous	6 5	8 7
Event Characteristics		**Number of Events=12**	**Number of Events=16**
Seriousness (Event Level)[c]	Serious	12	16
Outcome (Event Level)[c]	Not resolved Resolved Resolving NR	3 3 2 4	3 7 2 4

Key: NR=Not Reported
a: The calculation was based on the current reporting period (25 February 2022 to 24 August 2022).
b: Countries/Territories were presented in decreasing order for the current reporting period (25 February 2022 to 24 August 2022).
c: Seriousness and outcome have been presented for the events of interest. A single case may report more than 1 event of interest.

Of these 11 post-marketing, initial cases reported as booster, the most frequently reported countries/territories of origin (n≥3) were Germany (n=4), followed by Brazil and the US (n=3 each). These cases concerned 7 females, 3 males, and 1 did not report sex. The age range was from 20 to 56 years.

The frequency distribution of the MedDRA PTs of interest reported in post-marketing cases reported as booster is presented in Table 128 below. A single case may contain more than 1 EOI.

Table 128: Frequency of MedDRA PTs of Interest in Post-marketing Cases Reported as Booster Dose With the Use of Ad26.COV2.S and Reporting Generalised Convulsion

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Seizure	8	0	11	0
Epilepsy	3	0	4	0
Generalised tonic-clonic seizure	1	0	1	0

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: The MedDRA PTs of interest have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event of interest.

The EOI included seizure (n=8), epilepsy (n=3), and generalised tonic-clonic seizure (n=1). The mean and median TTO were 61.1 and 9.0 days, respectively. Where reported (n=8), the outcomes were not resolved and resolved (n=3 each) and resolving (n=2).

Fatal Post-marketing Booster Dose Cases

There were no fatal cases reported as booster which were retrieved from the search of the Company global safety database during the interval reporting period of 25 February 2022 to 24 August 2022.

Literature ICSR

No ICSR literature cases were received during the reporting period of 25 February 2022 to 24 August 2022.

O/E Analysis Results

Appendix 7.1 contains the methodology used to calculate and perform the O/E analyses for the AESI. Results of the restricted O/E and sensitivity analysis are presented in Table 129.

Table 129: Generalised Convulsions: Restricted O/E and Sensitivity Analysis Results – (Cumulative Through 24 August 2022)

Restricted 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	43.76	0.17	(0.12, 0.23)	0.38	(0.28, 0.52)

Key: CI=Confidence Interval; EOI=Event(s) of Interest; EU=European Union; LB=Lower Bound; O/E=Observed versus Expected; PE=Point Estimate; RP=Reporting Percentage; US=United States
a: Counts included EOI (from valid cases) that occurred within the risk window (Day: 1 to 14) only.
b: Poisson exact confidence interval (95% CI).

The EU restricted sensitivity analysis showed an O/E ratio of <1 for the 18 to 59 age group.

Results of the US and EU O/E analysis (both broad and restricted, where applicable) are provided in Appendix 7.2, this includes cumulative exposure, expected counts and background incidence rates.

Conclusion

Based on the evaluation of the cases, and review of safety from other sources, the information is consistent with the information known about generalised convulsion. The Company will continue to closely monitor generalised convulsion as an AESI.

16.3.6.3.2. Encephalitis, Including Acute Disseminated Encephalomyelitis and Meningoencephalitis

Introduction

Encephalitis, including acute disseminated encephalomyelitis and meningoencephalitis (ADEM) is listed as an AESI in the cRMP, EU RMP, and the US PVP.

Methods

The Company global safety database was searched for medically confirmed and medically unconfirmed cases received during this reporting period and cumulatively, which coded to the search criteria provided in Appendix 5.

An O/E analysis has been performed and information is presented in the O/E Analysis subsection below.

Results/Discussion

Primary Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 11 (8 medically confirmed and 3 medically unconfirmed) initial, primary dose cases reporting encephalitis, including ADEM and meningoencephalitis were identified. All 11 cases were serious and reported a total of 12 serious EOI.

All 11 primary dose cases received during the interval were reported from post-marketing sources (including spontaneous and solicited). No cases were reported from Janssen Sponsored Clinical Studies or Janssen Supported Clinical Studies.

Cumulatively, 88 (62 medically confirmed and 26 medically unconfirmed) primary dose cases reporting encephalitis, including ADEM and meningoencephalitis were identified. All 88 cases were serious and reported a total of 92 serious EOI.

Of the 88 cumulative primary dose cases received, 2 were reported from Janssen Sponsored Clinical Studies, 3 from Janssen Supported Clinical Studies, and 83 from post-marketing sources (including spontaneous and solicited cases).

Janssen Sponsored and Janssen Supported Clinical Studies (Primary Dose Cases)

There were no initial, primary dose cases retrieved from the search of the Company global safety database during the reporting period of 25 February 2022 to 24 August 2022 for either the Janssen Sponsored or Janssen Supported Clinical Studies.

Post-marketing Sources (Including Spontaneous and Solicited) Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 11 post-marketing sources (including spontaneous and solicited), initial, primary dose cases reporting encephalitis, including ADEM and meningoencephalitis were retrieved. These 11 post-marketing, initial, primary dose cases reported 12 serious EOI.

Cumulatively, 83 (57 medically confirmed and 26 medically unconfirmed) post-marketing, primary dose cases reporting encephalitis, including ADEM and meningoencephalitis were identified. All 83 cases were serious and reported a total of 87 serious EOI.

An overview of these cases is presented in Table 130 below.

Table 130: Characteristics of Post-marketing, Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Encephalitis, Including ADEM and Meningoencephalitis

Case Characteristics		Number of Cases Received During the Interval Reporting Period=11	Number of Cases Received Cumulatively=83
Sex	Female	5	36
	Male	4	42
	NR	2	5
Age (Years)[a]	<18	1	2
Minimum: 17	18 to 35	3	19
Maximum: 65	36 to 50	4	41
Mean: 37.5	51 to 64	1	7
Median: 41.5	≥65	1	7
	Adult	0	1
	NR	1	6
Sources	Spontaneous	11	83
Country/Territory[b]	Germany	3	19
	United States	2	22
	Croatia	1	1
	Greece	1	1
	Poland	1	1
	Romania	1	1
	South Africa	1	1
	United Kingdom	1	1
Event Characteristics		**Number of Events=12**	**Number of Events=87**
Seriousness (Event Level)[c]	Serious	12	87
	Not resolved	3	24
	Resolving	2	8

Table 130: Characteristics of Post-marketing, Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Encephalitis, Including ADEM and Meningoencephalitis

Case Characteristics		Number of Cases Received During the Interval Reporting Period=11	Number of Cases Received Cumulatively=83
Outcome (Event Level)[c]	Fatal	1	2
	Resolved	1	9
	Resolved with sequelae	1	4
	NR	4	40

Key: ADEM=Acute Disseminated Encephalomyelitis; NR=Not Reported
a: The calculation was based on the current reporting period (25 February 2022 to 24 August 2022). Age group was presented for cases where age was not reported.
b: Countries/Territories were presented in decreasing order for the current reporting period (25 February 2022 to 24 August 2022).
c: Seriousness and outcome have been presented for the events of interest. A single case may report more than 1 event of interest.

Of these 11 post-marketing, initial, primary dose cases, the most frequently reported countries/territories of origin (n≥2) were Germany (n=3), followed by the US (n=2). These cases concerned 5 females, 4 males, and 2 did not report sex. The age range was from 17 to 65 years.

The frequency distribution of the MedDRA PTs of interest reported in post-marketing, primary dose cases is presented in Table 131 below. A single case may contain more than 1 EOI.

Table 131: Frequency of MedDRA PTs of Interest in Post-marketing, Primary Dose Cases Reporting Encephalitis, Including ADEM and Meningoencephalitis With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Acute disseminated encephalomyelitis	4	0	18	0
Encephalitis	2	0	40	0
Encephalomyelitis	2	0	9	0
Noninfective encephalitis	2	0	12	0
Encephalitis haemorrhagic	1	0	1	0
Limbic encephalitis	1	0	2	0

Key: ADEM=Acute Disseminated Encephalomyelitis; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: The MedDRA PTs of interest have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event of interest.

The EOI (≥2) included acute disseminated encephalomyelitis (n=4) and encephalitis, encephalomyelitis, and noninfective encephalitis (n=2 each). The mean and median TTO were 22.5 and 12.0 days respectively. Where reported (n=8), the outcomes were not resolved (n=3), resolving (n=2), and fatal, resolved, and resolved with sequelae (n=1 each).

Fatal Post-marketing Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 1 post-marketing, initial, primary dose fatal case with 1 fatal EOI was retrieved. This literature case report concerned a 45-year-old male with a history of diabetes mellitus who experienced haemorrhagic encephalitis along with Tolosa-Hunt syndrome and infectious/autoimmune vasculitis on an unspecified day post-vaccination. The patient was reported as positive for SARS-CoV-2 by transcription-polymerase chain reaction. Considering the lack of information on temporal relationship for the EOI and the patient's serious underlying conditions, including COVID-19 infection, causal association with vaccination is unlikely.

Booster Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 2 (no medically confirmed and 2 medically unconfirmed) initial cases reported as booster were identified. Both cases were serious and reported a total of 2 serious EOI. Of these cases, 1 was heterologous and 1 was homologous.

Both cases reported as booster during the interval were from post-marketing sources (including spontaneous and solicited). No cases were reported from Janssen Sponsored Clinical Studies or Janssen Supported Clinical Studies.

Cumulatively, the aforementioned 2 medically unconfirmed cases reported as booster were identified.

A cumulative booster dose CIOMS II LL is presented in Appendix 8.6.

Janssen Sponsored and Janssen Supported Clinical Studies (Booster Dose Cases)

There were no initial cases reported as booster which were retrieved from the search of the Company global safety database during the interval reporting period of 25 February 2022 to 24 August 2022 for either the Janssen Sponsored or Janssen Supported Clinical Studies.

Post-marketing Sources (Including Spontaneous and Solicited) Booster Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 2 post-marketing sources (including spontaneous and solicited), initial cases reported as booster were retrieved. These 2 post-marketing, initial, booster dose cases reported 2 serious EOI.

Of these 2 post-marketing, booster dose cases, 1 case concerned a 76-year-old female from [redacted] and the second case concerned a 52-year-old male from [redacted] The EOI included acute disseminated encephalomyelitis and encephalitis. The mean and median TTO was 7.5 days. Where reported (n=1), the outcome was not resolved.

Cumulatively, the aforementioned 2 medically unconfirmed post-marketing cases reported as booster were identified.

Fatal Post-marketing Booster Dose Cases

There were no initial, fatal cases reported as booster which were retrieved from the search of the Company global safety database during the interval reporting period of 25 February 2022 to 24 August 2022.

Literature ICSR

ICSR literature cases received during the reporting period of 25 February 2022 to 24 August 2022 were reviewed, and no information was identified that would change the characterisation of risk.

O/E Analysis Results

Appendix 7.1 contains the methodology used to calculate and perform the O/E analyses for the AESI. Results of the restricted O/E and sensitivity analysis for encephalitis and ADEM are presented in Table 132.

PRAC endorsed (Procedure Number: EMEA/H/C/PSUSA/00010916/202202) the removal of "*SMQ' "Noninfectious Encephalopathy/Delirium" and "Noninfectious meningitis*" for the MedDRA O/E search strategy. The O/E MedDRA search strategy for Encephalitis was updated to Noninfectious Encephalitis SMQ (Narrow) only.

Table 132: Encephalitis, ADEM Alone: Restricted O/E and Sensitivity Analysis Results (Cumulative Through 24 August 2022)

		Restricted O/E Analysis				Sensitivity Analysis	
AESI	**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)**	
Encephalitis	**US**	18 to 59	13.30	0.11	(0.06, 0.18)	1.84	(0.99, 3.13)
		≥60	3.68	0.04	(0.01, 0.11)	0.65	(0.16, 1.73)
	EU	18 to 59	20.00	0.14	(0.09, 0.22)	2.42	(1.48, 3.74)
ADEM	**US**	18 to 59	7.65	0.61	(0.26, 1.22)	3.18	(1.34, 6.36)
	EU	18 to 59	4.00	0.28	(0.08, 0.72)	1.45	(0.40, 3.72)

Key: ADEM=Acute disseminated encephalomyelitis; CI=Confidence Interval; EU=European Union; EOI=Event(s) of Interest; LB=Lower Bound; O/E=Observed versus Expected; PE=Point Estimate; RP=Reporting Percentage; US=United States

a: Counts included EOI (from valid cases) that occurred within the risk window (Day: 1 to 42) only.

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

Encephalitis

The US restricted sensitivity analysis showed an O/E ratio of >1 for the 18 to 59 age group only. This O/E ratio was not statistically significant above 1 (lower bound of 95% confidence interval <1). The EU restricted sensitivity analysis showed an O/E ratio of >1 in the 18 to 59 age group. This O/E ratio was statistically significant above 1 (lower bound of 95% confidence interval >1). Since the previous PBRER DLP (24 February2022), the US ≥60 age group restricted sensitivity O/E ratio changed from >1 to <1. This was attributed to the change in the MedDRA search strategy for Encephalitis.

ADEM

The US restricted sensitivity analysis showed an O/E ratio of >1 for the 18 to 59 age group. This O/E ratio was statistically significant above 1 (lower bound of 95% confidence interval >1). The EU restricted sensitivity analysis showed an O/E ratio of >1 for the 18 to 59 age group. This O/E ratio was not statistically significant above 1 (lower bound of 95% confidence interval <1). Since the previous PBRER DLP (24 February 2022), for the EU 18 to 59 age group, the restricted sensitivity O/E ratio showed an increase from <1 to >1. The O/E ratio was not statistically significant above 1 (lower bound of 95% confidence interval >1).

Results of the US and EU O/E analysis (both broad and restricted, where applicable) are provided in Appendix 7.2, this includes cumulative exposure, expected counts and background incidence rates.

Conclusion

Based on the evaluation of the cases, and review of safety from other sources, the information is consistent with the information known about encephalitis, including ADEM and meningoencephalitis. The Company will continue to closely monitor cases of encephalitis, including ADEM and meningoencephalitis, as an AESI.

16.3.6.3.3. Multiple Sclerosis (Including Optic Neuritis)

Introduction

Multiple sclerosis, including optic neuritis is listed as an AESI in the cRMP, EU RMP, and the US PVP.

Methods

The Company global safety database was searched for medically confirmed and medically unconfirmed cases received during this reporting period and cumulatively, which coded to the search criteria provided in Appendix 5.

An O/E analysis has been performed and information is presented in the O/E analysis subsection below.

Results/Discussion

Primary Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 14 (8 medically confirmed and 6 medically unconfirmed) initial, primary dose cases reporting multiple sclerosis, including optic neuritis were identified. All 14 cases were serious and reported a total of 14 serious EOI.

Of these 14 initial, primary dose cases received during the interval reporting period, 2 were reported from Janssen Sponsored Clinical Studies and 12 from post-marketing sources (including spontaneous and solicited). No cases were reported from Janssen Supported Clinical Studies.

Cumulatively, 71 (37 medically confirmed and 34 medically unconfirmed) primary dose cases reporting multiple sclerosis, including optic neuritis were identified. All 71 cases were serious and reported a total of 73 serious EOI.

Of the 71 cumulative primary dose cases received, 3 were reported from Janssen Sponsored Clinical Studies, 1 from a Janssen Supported Clinical Study, and 67 from post-marketing sources (including spontaneous and solicited cases).

Janssen Sponsored Clinical Studies Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 2 initial, primary dose cases reporting multiple sclerosis, including optic neuritis were retrieved from Janssen Sponsored Clinical Studies. Both cases were from VAC31518COV3001. These 2 cases reported 2 serious EOI. The reported country/territory of origin was [redacted] Both cases concerned females. The age was reported as 47 and 66 years.

The EOI included multiple sclerosis (n=2). The mean and median TTO were 388.5 days each. The outcomes for the reported EOI were resolved (n=1) and resolving (n=1).

Janssen Supported Clinical Studies Primary Dose Cases

There were no initial, primary dose cases retrieved from the search of the Company global safety database during the reporting period of 25 February 2022 to 24 August 2022.

Post-marketing Sources (Including Spontaneous and Solicited) Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 12 post-marketing sources (including spontaneous and solicited), initial, primary dose cases reporting multiple sclerosis, including optic neuritis were retrieved. These 12 initial, post-marketing, primary dose cases reported 12 serious EOI.

Cumulatively, 67 (33 medically confirmed and 34 medically unconfirmed) post-marketing, primary dose cases reporting multiple sclerosis, including optic neuritis were identified. All 67 cases were serious and reported a total of 69 serious EOI.

An overview of these cases is presented in Table 133 below.

Table 133: Characteristics of Post-marketing, Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Multiple Sclerosis, Including Optic Neuritis

Case Characteristics		Number of Cases Received During the Interval Reporting Period=12	Number of Cases Received Cumulatively=67
Sex	Male	7	28
	Female	4	36
	NR	1	3

Table 133: Characteristics of Post-marketing, Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Multiple Sclerosis, Including Optic Neuritis

Case Characteristics		Number of Cases Received During the Interval Reporting Period=12	Number of Cases Received Cumulatively=67
Age (Years)[a] **Minimum: 21** **Maximum: 65** **Mean: 41.8** **Median: 39**	18 to 35	3	18
	36 to 50	6	28
	51 to 64	1	12
	≥65	1	3
	Adult	1	1
	NR	0	5
Sources	Spontaneous	12	66
	Clinical study (noninterventional; solicited)	0	1
Country/Territory[b]	Germany	4	9
	United States	3	38
	Poland	2	2
	Austria	1	1
	Czech Republic	1	2
	Greece	1	4
Event Characteristics		**Number of Events=12**	**Number of Events=69**
Seriousness (Event Level)[c]	Serious	12	69
Outcome (Event Level)[c]	Not resolved	4	45
	Resolving	2	5
	Resolved	1	5
	Resolved with sequelae	0	3
	NR	5	11

Key: NR=Not Reported

a: The calculation was based on the current reporting period (25 February 2022 to 24 August 2022). Age group was presented for cases where age was not reported.

b: Countries/Territories were presented in decreasing order for the current reporting period (25 February 2022 to 24 August 2022).

c: Seriousness and outcome have been presented for the events of interest. A single case may report more than 1 event of interest.

Of these 12 post-marketing, initial, primary dose cases, the most frequently reported countries/territories of origin (≥2) were Germany (n=4), followed by the US (n=3) and Poland (n=2). These cases concerned 7 males, 4 females, and 1 did not report sex. The age range was from 21 to 65 years.

The frequency distribution of the MedDRA PTs of interest reported in post-marketing, primary dose cases is presented in Table 134 below.

Table 134: Frequency of MedDRA PTs of Interest in Post-marketing, Primary Dose Cases Reporting Multiple Sclerosis, Including Optic Neuritis With the Use of Ad26.COV2.S

MedDRA PTs	Number of Serious Events Reported During the Interval Reporting Period[a]	Number of Serious Events Reported Cumulatively
Multiple sclerosis	5	33
Multiple sclerosis relapse	4	10
Optic neuritis	3	25

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: The MedDRA PTs of interest have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022).

The EOI included multiple sclerosis (n=5), multiple sclerosis relapse (n=4), and optic neuritis (n=3). The mean and median TTO were 42.9 and 10 days, respectively. Where reported (n=7), the outcomes were not resolved (n=4), resolving (n=2), and resolved (n=1).

Fatal Post-marketing Primary Dose Cases

There were no fatal post-marketing, initial, primary dose cases retrieved from the search of the Company global safety database during the interval reporting period of 25 February 2022 to 24 August 2022.

Booster Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 5 (3 medically confirmed and 2 medically unconfirmed) initial cases reported as booster were identified. All 5 cases were serious and reported a total of 7 serious EOI. Of these cases, 3 were heterologous and 2 were homologous.

All 5 booster cases reported as booster during the interval were reported from post-marketing spontaneous sources. No cases were reported from Janssen Sponsored Clinical Studies or Janssen Supported Clinical Studies.

Cumulatively, the aforementioned 5 (3 medically confirmed and 2 medically unconfirmed) cases reported as booster were identified.

A cumulative booster dose CIOMS II LL is presented in Appendix 8.7.

Janssen Sponsored and Janssen Supported Clinical Studies (Booster Dose Cases)

There were no initial cases reported as booster which were retrieved from the search of the Company global safety database during the interval reporting period of 25 February 2022 to 24 August 2022 for either the Janssen Sponsored or Janssen Supported Clinical Studies.

Post-marketing Sources (Including Spontaneous and Solicited) Booster Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 5 post-marketing sources cases (spontaneous), initial cases reported as booster were retrieved. These 5 post-marketing, initial, booster dose cases reported 7 serious EOI.

Cumulatively, the aforementioned 5 (3 medically confirmed and 2 medically unconfirmed) post-marketing cases reported as booster were identified.

An overview of these cases is presented in Table 135 below.

Table 135: Characteristics of Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Multiple Sclerosis, Including Optic Neuritis

Case Characteristics		Number of Cases Received During the Interval Reporting Period=5	Number of Cases Received Cumulatively=5
Sex	Male	4	4
	Female	1	1
Age (Years)[a] **Minimum: 22** **Maximum: 37** **Mean: 28.8** **Median: 29**	18 to 35	4	4
	36 to 50	1	1
Country/Territory[b]	Germany	3	3
	Greece	1	1
	United States	1	1
Sources	Spontaneous	5	5
Classification	Heterologous	3	3
	Homologous	2	2
Event Characteristics		**Number of Events=7**	**Number of Events=7**
Seriousness (Event Level)[c]	Serious	7	7
Outcome (Event Level)[c]	Not resolved	5	5
	Resolved with sequelae	1	1
	Resolving	1	1

a: The calculation was based on the current reporting period (25 February 2022 to 24 August 2022).
b: Countries/Territories were presented in decreasing order for the current reporting period (25 February 2022 to 24 August 2022).
c: Seriousness and outcome have been presented for the events of interest. A single case may report more than 1 event of interest.

The reported countries/territories of origin in these post-marketing cases reported as booster were Germany (n=3), followed by Greece and the US (n=1 each). These cases concerned 4 males and 1 female. The age range was from 22 to 37 years.

The frequency distribution of the MedDRA PTs of interest reported in post-marketing cases reported as booster is presented in Table 136 below. A single case may contain more than 1 EOI.

Table 136: Frequency of MedDRA PTs of Interest in Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Multiple Sclerosis, Including Optic Neuritis

MedDRA PTs	Number of Serious Events Reported During the Interval Reporting Period[a]	Number of Serious Events Reported Cumulatively
Optic neuritis	4	4
Multiple sclerosis	3	3

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: The MedDRA PTs of interest have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event of interest.

The EOI included optic neuritis (n=4) and multiple sclerosis (n=3). The mean and median TTO were 170.2 and 229 days, respectively. The reported outcomes were not resolved (n=5), and resolved with sequelae and resolving (n=1 each).

Fatal Post-marketing Booster Dose Cases

There were no fatal post-marketing initial cases reported as booster which were retrieved from the search of the Company global safety database during the interval reporting period of 25 February 2022 to 24 August 2022.

Literature ICSR

ICSR literature cases received during the reporting period of 25 February 2022 to 24 August 2022 were reviewed, and no information was identified that would change the characterisation of risk.

Discussion

Review of the cases, including demographics, concomitant medications, concurrent conditions/medical history, outcome, and seriousness received during this reporting period is consistent with what is currently known about multiple sclerosis, including optic neuritis.

O/E Analysis Results

Appendix 7.1 contains the methodology used to calculate and perform the O/E analyses for the AESI.

Since the previous PBRER data lock point (24 February 2022), the broad O/E ratio has remained <1 in the US and EU for both age groups. A restricted O/E analysis with sensitivity analysis was not required.

Results of the US and EU O/E analysis (both broad and restricted, where applicable) are provided in Appendix 7.2, this includes cumulative exposure, expected counts and background incidence rates.

Conclusion

Based on the evaluation of the cases, and review of safety from other sources, the information is consistent with the information known about multiple sclerosis, including optic neuritis. The Company will continue to closely monitor multiple sclerosis, including optic neuritis as an AESI.

16.3.6.3.4. Narcolepsy

Introduction

Narcolepsy is listed as an AESI in the cRMP, EU RMP, and the US PVP.

In the PRAC assessment for the PBRER covering the reporting period from 25 August 2021 to 24 February 2022, the rapporteur concluded that, narcolepsy is an event which will take long to be identified, thus required the Company to be monitor and present the topic in upcoming PBRERs and to "*focus on cases that could be true cases of narcolepsy*".

Methods

The Company global safety database was searched for medically confirmed and medically unconfirmed cases received during this reporting period and cumulatively, which coded to the search criteria provided in Appendix 5.

An O/E analysis has been performed and information is presented in the O/E Analysis subsection below.

Results/Discussion

Primary Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 126 (14 medically confirmed and 112 medically unconfirmed) initial, primary dose cases reporting narcolepsy were identified. Of these 126 cases, 41 were serious and 85 were nonserious and reported a total of 133 EOI (29 serious; 104 nonserious).

All 126 primary dose cases received during the interval reporting period were reported from post-marketing sources (including spontaneous and solicited). No cases were reported from Janssen Sponsored Clinical Studies or Janssen Supported Clinical Studies.

Cumulatively, 564 (77 medically confirmed and 487 medically unconfirmed) primary dose cases reporting narcolepsy were identified. Of these cases, 183 were serious and 381 were nonserious and reported a total of 572 EOI (91 serious; 481 nonserious).

Of the 564 cumulative primary dose cases received, 1 was reported from a Janssen Supported Clinical Study and 563 were from post-marketing sources (including spontaneous and solicited cases). No cases were reported from Janssen Sponsored Clinical Studies.

Janssen Sponsored and Janssen Supported Clinical Studies (Primary Dose Cases)

There were no initial, primary dose cases retrieved from the search of the Company global safety database during the reporting period of 25 February 2022 to 24 August 2022 for either the Janssen Sponsored or Janssen Supported Clinical Studies.

Post-marketing Sources (Including Spontaneous and Solicited) Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 126 post-marketing sources (including spontaneous and solicited), initial, primary dose cases reporting narcolepsy were retrieved. These 126 post-marketing, initial, primary dose cases reported 133 EOI (29 serious; 104 nonserious).

Cumulatively, 563 (76 medically confirmed and 487 medically unconfirmed) post-marketing, primary dose cases reporting narcolepsy were identified. Of these cases, 183 were serious and 380 were nonserious and reported a total of 571 EOI (91 serious; 480 nonserious).

An overview of these cases is presented in Table 137 below.

Table 137: Characteristics of Post-marketing, Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Narcolepsy

Case Characteristics		Number of Cases Received During the Interval Reporting Period=126	Number of Cases Received Cumulatively=563
Sex	Male	65	233
	Female	59	285
	NR	2	45
Age (Years)[a]	18 to 35	36	120
Minimum: 18	36 to 50	53	140
Maximum: 78	51 to 64	30	146
Mean: 42.7	≥65	5	68
Median: 42	Adult	0	5
	NR	2	84
Sources	Spontaneous	110	533
	Clinical study (noninterventional; solicited)	16	30
Country/Territory[b]	Germany	80	134
	United States	11	298
	Poland	9	17
	Austria	6	12
	Belgium	3	14
	Latvia	3	7

Table 137: Characteristics of Post-marketing, Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Narcolepsy

Case Characteristics		Number of Cases Received During the Interval Reporting Period=126	Number of Cases Received Cumulatively=563
	Switzerland	3	5
	Cote d'Ivoire	2	2
	France	2	9
	Ireland	2	9
	Spain	2	9
Event Characteristics		**Number of Events=133**	**Number of Events=571**
Seriousness (Event Level)[c]	Nonserious	104	480
	Serious	29	91
Outcome (Event Level)[c]	Not resolved	61	204
	Resolving	28	62
	Resolved	21	119
	Resolved with sequelae	7	7
	Fatal	0	1
	NR	16	178

Key: NR=Not Reported
a: The calculation was based on the current reporting period (25 February 2022 to 24 August 2022). Age group was presented for cases where age was not reported.
b: Countries/Territories with frequency ≥2 were presented in decreasing order for the current reporting period (25 February 2022 to 24 August 2022).
c: Seriousness and outcome have been presented for the events of interest. A single case may report more than 1 event of interest.

Of these 126 post-marketing, initial primary dose cases, the most frequently reported countries/territories of origin (≥9) were Germany (n=80), followed by the US (n=11), and Poland (n=9). These cases concerned 65 males, 59 females, and 2 did not report sex. The age range was from 18 to 78 years.

The frequency distribution of the MedDRA PTs of interest reported in post-marketing, primary dose cases is presented in Table 138 below. A single case may contain more than 1 EOI.

Table 138: Frequency of MedDRA PTs of Interest in Post-marketing, Primary Dose Cases Reporting Narcolepsy With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Sleep disorder	26	91	69	270
Hypersomnia	2	13	18	210
Sudden onset of sleep	1	0	1	0

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: The MedDRA PTs of interest have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event of interest.

The EOI included sleep disorder (n=117), hypersomnia (n=15), and sudden onset of sleep (n=1). The mean and median TTO were 8.9 days and 1 day, respectively. Where reported (n=117), the outcomes were not resolved (n=61), resolving (n=28), resolved (n=21), and resolved with sequelae (n=7).

Fatal Post-marketing Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 1 post-marketing, initial, primary dose fatal case with no fatal EOI was retrieved.

Booster Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 14 initial cases reported as booster were identified. There were 4 serious and 10 nonserious cases and reported a total of 15 EOI (1 serious; 14 nonserious). Of these cases, 10 were heterologous and 4 were homologous.

All 14 initial cases reported as booster during the interval were from post-marketing sources (including spontaneous and solicited). No cases were reported from Janssen Sponsored Clinical Studies or Janssen Supported Clinical Studies.

Cumulatively, 31 (3 medically confirmed and 28 medically unconfirmed) cases reported as booster were identified. Of these cases, 11 were serious and 20 were nonserious and reported a total of 32 EOI (4 serious; 28 nonserious). Of these cases, 16 were heterologous and 15 were homologous.

All 31 cumulative booster dose cases received were reported from post-marketing sources (including spontaneous and solicited cases). No cases were reported from Janssen Sponsored Clinical Studies or Janssen Supported Clinical Studies.

A cumulative booster dose CIOMS II LL is presented in Appendix 8.8.

Janssen Sponsored and Janssen Supported Clinical Studies (Booster Dose Cases)

There were no initial cases reported as booster which were retrieved from the search of the Company global safety database during the interval reporting period of 25 February 2022 to 24 August 2022 for either the Janssen Sponsored or Janssen Supported Clinical Studies.

Post-marketing Sources (Including Spontaneous and Solicited) Booster Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 14 post-marketing sources (including spontaneous and solicited), initial cases reported as booster were retrieved. These 14 post-marketing, initial, booster dose cases reported 15 EOI (1 serious; 14 nonserious).

Cumulatively, 31 (3 medically confirmed and 28 medically unconfirmed) post-marketing cases reported as booster were identified. Of these cases, 11 were serious and 20 were nonserious and reported a total of 32 EOI (4 serious; 28 nonserious).

An overview of these cases is presented in Table 139 below.

Table 139: Characteristics of Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Narcolepsy

Case Characteristics		Number of Cases Received During the Interval Reporting Period=14	Number of Cases Received Cumulatively=31
Sex	Female	9	20
	Male	5	9
	NR	0	2
Age (Years)[a]	18 to 35	5	8
Minimum: 20	36 to 50	6	10
Maximum: 59	51 to 64	3	8
Mean: 40	≥65	0	2
Median: 38.5	NR	0	3
Country/Territory[b]	Germany	9	9
	Austria	2	2
	Brazil	2	4
	United States	1	12
Sources	Spontaneous	12	29
	Clinical study (noninterventional; solicited)	2	2
Classification	Heterologous	10	16
	Homologous	4	15
Event Characteristics		**Number of Events=15**	**Number of Events=32**
Seriousness (Event Level)[c]	Nonserious	14	28
	Serious	1	4
Outcome (Event Level)[c]	Not resolved	12	15
	Resolving	2	2
	Resolved with sequelae	1	1
	Resolved	0	6
	NR	0	8

Key: NR=Not Reported

a: The calculation was based on the current reporting period (25 February 2022 to 24 August 2022).

b: Countries/Territories were presented in decreasing order for the current reporting period (25 February 2022 to 24 August 2022).

c: Seriousness and outcome have been presented for the events of interest. A single case may report more than 1 event of interest.

Of these 14 post-marketing, initial cases reported as booster, the most frequently reported countries/territories of origin (≥2) were Germany (n=9), followed by Austria and Brazil (n=2 each). These cases concerned 9 females and 5 males. The age range was from 20 to 59 years.

The frequency distribution of the MedDRA PTs of interest reported in post-marketing cases reported as booster is presented in Table 140 below. A single case may contain more than 1 EOI.

Table 140: Frequency of MedDRA PTs of Interest in Post-marketing Cases Reported as Booster Dose With the Use of Ad26.COV2.S and Reporting Narcolepsy

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Sleep disorder	1	12	3	18
Hypersomnia	0	2	1	10

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

a: The MedDRA PTs of interest have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event of interest.

The EOI included sleep disorder (n=13) and hypersomnia (n=2). The mean and median TTO were 100.2 and 2 days, respectively. The reported outcomes were not resolved (n=12), resolving (n=2), and resolved with sequelae (n=1).

Fatal Post-marketing Booster Dose Cases

There were no initial, fatal cases reported as booster which were retrieved from the search of the Company global safety database during the interval reporting period of 25 February 2022 to 24 August 2022.

Literature ICSR

ICSR literature cases received during the reporting period of 25 February 2022 to 24 August 2022 were reviewed, and no information was identified that would change the characterisation of risk.

Discussion

Upon review of the interval and cumulative data, no new safety information was identified regarding this AESI. Most of the cases reported hypersomnia and sleep disorder, which are not indicative of narcolepsy.

O/E Analysis Results

No cases meeting the definition of narcolepsy have been identified during the reporting period. Therefore, no O/E analysis was performed for this AESI.

Conclusion

Based on the evaluation of the cases, and review of safety from other sources, the information is consistent with the information known about narcolepsy. The Company will continue to closely monitor narcolepsy as an AESI.

16.3.6.3.5. Sensorineural Hearing Loss

Introduction

Sensorineural hearing loss (SNHL) is listed as an AESI in the cRMP, EU RMP, and the US PVP.

According to the PRAC FAR (PRAC AR 2022) for the Ad26.COV2.S PBRER (EMEA/H/C/PSUSA/00010916/202202) received on 29 September 2022: *"Removing tinnitus from the search strategy is endorsed."*

Methods

The Company global safety database was searched for medically confirmed and medically unconfirmed cases received during this reporting period and cumulatively, which coded to the search criteria provided in Appendix 5.

An O/E analysis has been performed and information is presented in the O/E Analysis subsection below.

Results/Discussion

Primary Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 56 (11 medically confirmed and 45 medically unconfirmed) initial, primary dose cases reporting SNHL were identified. Of these 56 cases, 43 were serious and 13 were nonserious and reported a total of 58 EOI (44 serious; 14 nonserious).

Of these 56 primary dose cases received during the interval reporting period, 1 was reported from a Janssen Sponsored Clinical Study and 55 were from post-marketing sources (including spontaneous and solicited). No cases were reported from Janssen Supported Clinical Studies.

Cumulatively, 234 (55 medically confirmed and 179 medically unconfirmed) primary dose cases reporting SNHL were identified. Of these cases, 176 were serious and 58 were nonserious and reported a total of 244 EOI (174 serious; 70 nonserious).

Of the 234 cumulative primary dose cases received, 2 were reported from Janssen Sponsored Clinical Studies, 1 was from a Janssen Supported Clinical Study, and 231 were from post-marketing sources (including spontaneous and solicited cases).

Janssen Sponsored Clinical Studies Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 1 initial, primary dose case reporting SNHL was retrieved from a Janssen Sponsored Clinical Study. This case was from VAC31518COV3009 and concerned a 50-year-old male from [redacted] who experienced a serious EOI of deafness neurosensory. The reported TTO was 252 days and the reported outcome was not resolved.

Janssen Supported Clinical Studies Primary Dose Cases

There were no initial, primary dose cases retrieved from the search of the Company global safety database during the reporting period of 25 February 2022 to 24 August 2022.

Post-marketing Sources (Including Spontaneous and Solicited) Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 55 post-marketing sources (including spontaneous and solicited), initial, primary dose cases reporting SNHL were retrieved. These 55 post-marketing, primary dose cases reported 57 EOI (43 serious; 14 nonserious).

Cumulatively, 231 (52 medically confirmed and 179 medically unconfirmed) post-marketing, primary dose cases reporting SNHL were identified. Of these cases, 173 were serious and 58 were nonserious and reported a total of 241 EOI (171 serious; 70 nonserious).

An overview of these cases is presented in Table 141 below.

Table 141: Characteristics of Post-marketing, Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Sensorineural Hearing Loss

Case Characteristics		Number of Cases Received During the Interval Reporting Period=55	Number of Cases Received Cumulatively=231
Sex	Female	30	116
	Male	22	104
	NR	3	11
Age (Years)[a]	<18	0	1
Minimum: 19	18 to 35	21	50
Maximum: 90	36 to 50	16	57
Mean: 43.1	51 to 64	14	71
Median: 42	≥65	3	27
	Adult	1	3
	Elderly	0	1
	NR	0	21
Sources	Spontaneous	42	208
	Clinical study (noninterventional; solicited)	13	23
Country/Territory[b]	Germany	30	55
	United States	7	78
	France	5	13
	Poland	3	7
	South Africa	3	4
	Belgium	2	9
	Austria	1	4
	Ireland	1	7
	Italy	1	9

Table 141: Characteristics of Post-marketing, Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Sensorineural Hearing Loss

Case Characteristics		Number of Cases Received During the Interval Reporting Period=55	Number of Cases Received Cumulatively=231
	Latvia	1	2
	Romania	1	2
Event Characteristics		**Number of Events=57**	**Number of Events=241**
Seriousness (Event Level)[c]	Serious	43	171
	Nonserious	14	70
Outcome (Event Level)[c]	Not resolved	27	118
	Resolving	12	41
	Resolved	6	34
	Resolved with sequelae	5	8
	NR	7	40

Key: NR=Not Reported
a: The calculation was based on the current reporting period (25 February 2022 to 24 August 2022). Age group was presented for cases where age was not reported.
b: Countries/Territories were presented in decreasing order for the current reporting period (25 February 2022 to 24 August 2022).
c: Seriousness and outcome have been presented for the events of interest. A single case may report more than 1 event of interest.

Of these 55 post-marketing, primary dose cases, the most frequently reported countries/territories of origin (≥5) were Germany (n=30), followed by the US (n=7) and France (n=5). These cases concerned 30 females, 22 males, and 3 did not report sex. The age range was from 19 to 90 years.

The frequency distribution of the MedDRA PTs of interest reported in post-marketing, primary dose cases is presented in Table 142 below. A single case may contain more than 1 EOI.

Table 142: Frequency of MedDRA PTs of Interest in Post-marketing, Primary Dose Cases Reporting Sensorineural Hearing Loss With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Deafness	28	0	80	0
Hypoacusis	4	12	34	63
Deafness unilateral	5	0	24	0
Vestibular neuronitis	3	0	14	1
Auditory disorder	0	2	2	6
Deafness bilateral	1	0	2	0
Deafness neurosensory	1	0	9	0
Deafness transitory	1	0	4	0

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: The MedDRA PTs of interest have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event of interest.

The EOI (≥3) included deafness (n=28), hypoacusis (n=16), deafness unilateral (n=5), and vestibular neuronitis (n=3). The mean and median TTO were 22.6 and 3 days respectively. Where reported (n=50), the outcomes were not resolved (n=27), resolving (n=12), resolved (n=6), and resolved with sequelae (n=5).

Fatal Post-marketing Primary Dose Cases

There were no initial, fatal post-marketing primary dose cases retrieved from the search of the Company global safety database during the interval reporting period of 25 February 2022 to 24 August 2022.

Booster Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 8 initial cases (all medically unconfirmed cases) reported as booster were identified. Although 1 medically unconfirmed case was reported as a booster, it was determined to be a primary dose case upon further review and has been captured in the primary dose subsection above. Of the remaining 7 cases (all medically unconfirmed cases), 2 were serious and 5 were nonserious and reported a total of 7 EOI (2 serious; 5 nonserious). Of these cases, 3 were homologous and 4 were heterologous.

All 7 initial cases reported as booster during the interval were from post-marketing sources (including spontaneous and solicited). No cases were reported from Janssen Sponsored Clinical Studies or Janssen Supported Clinical Studies.

Cumulatively, 10 (no medically confirmed and 10 medically unconfirmed) cases reported as booster were identified. Of these cases, 5 were serious and 5 were nonserious and reported a total of 10 EOI (4 serious; 6 nonserious). Of these cases, 5 were homologous and 5 were heterologous.

All 10 cumulative booster dose cases received were reported from post-marketing sources (including spontaneous and solicited cases). No cases were reported from Janssen Sponsored Clinical Studies or Janssen Supported Clinical Studies.

A cumulative booster dose CIOMS II LL is presented in Appendix 8.9.

Janssen Sponsored and Janssen Supported Clinical Studies (Booster Dose Cases)

There were no initial cases reported as booster which were retrieved from the search of the Company global safety database during the interval reporting period of 25 February 2022 to 24 August 2022 for either the Janssen Sponsored or Janssen Supported Clinical Studies.

Post-marketing Sources (Including Spontaneous and Solicited) Booster Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 7 post-marketing sources (including spontaneous and solicited), initial cases reported as booster were retrieved. These 7 post-marketing, initial, booster dose cases reported 7 EOI (2 serious; 5 nonserious).

Cumulatively, 10 (no medically confirmed and 10 medically unconfirmed) post-marketing cases reported as booster were identified. Of these cases, 5 were serious and 5 were nonserious and reported a total of 10 EOI (4 serious; 6 nonserious).

An overview of these cases is presented in Table 143 below.

Table 143: Characteristics of Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Sensorineural Hearing Loss

Case Characteristics		Number of Cases Received During the Interval Reporting Period=7	Number of Cases Received Cumulatively=10
Sex	Female	7	9
	Male	0	1
Age (Years)[a]	18 to 35	2	2
Minimum: 27	36 to 50	1	3
Maximum: 60	51 to 64	1	2
Mean: 41.8	NR	3	3
Median: 40			
Country/Territory[b]	Brazil	5	6
	Austria	1	1
	South Africa	1	1
Sources	Spontaneous	6	9
	Clinical study (noninterventional; solicited)	1	1
Classification	Heterologous	4	5
	Homologous	3	5
Event Characteristics		**Number of Events=7**	**Number of Events=10**
Seriousness (Event Level)[c]	Nonserious	5	6
	Serious	2	4
Outcome (Event Level)[c]	Resolving	2	2
	Not resolved	1	2
	Resolved	1	3
	Resolved with sequelae	1	1
	NR	2	2

Key: NR=Not Reported
a: The calculation was based on the current reporting period (25 February 2022 to 24 August 2022).
b: Countries/Territories were presented in decreasing order for the current reporting period (25 February 2022 to 24 August 2022).
c: Seriousness and outcome have been presented for the events of interest.

For these 7 post-marketing cases reported as booster, the reported countries/territories of origin were [redacted] (n=5), followed by [redacted] and [redacted] (n=1 each). These cases concerned 7 females. The age range was from 27 to 60 years.

The frequency distribution of the MedDRA PTs of interest reported in post-marketing cases reported as booster is presented in Table 144 below.

Table 144: Frequency of MedDRA PTs of Interest in Post-marketing Cases Reported as Booster Dose With the Use of Ad26.COV2.S and Reporting Sensorineural Hearing Loss

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Hypoacusis	0	5	1	6
Deafness unilateral	1	0	1	0
Vestibular neuronitis	1	0	1	0

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: The MedDRA PTs of interest have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022).

The EOI included hypoacusis (n=5), and deafness unilateral and vestibular neuronitis (n=1 each). The mean and median TTO were 4.8 days and 0.5 day, respectively. Where reported (n=5), the outcomes were resolving (n=2), and not resolved, resolved, and resolved with sequelae (n=1 each).

Fatal Post-marketing Booster Dose Cases

There were no initial fatal cases reported as booster which were retrieved from the search of the Company global safety database during the interval reporting period of 25 February 2022 to 24 August 2022.

Literature ICSR

ICSR literature cases received during the reporting period of 25 February 2022 to 24 August 2022 were reviewed, and no information was identified that would change the characterisation of risk.

Discussion

Most cases presented limited information for a meaningful medical assessment. Two primary dose cases specifically reported that the patient experienced SNHL during this interval, 1 from a Janssen Sponsored Clinical Study, and 1 from a spontaneous literature report. In the case from the Janssen Sponsored Clinical Study, the EOI was outside the 60-day risk window. In the literature case, the patient experienced sudden SNHL 7 days post-vaccination. Incomplete audiogram results were provided in this case, and baseline data was missing. Additionally, the authors of the article concluded that the findings of their study did not suggest an association between COVID-19 vaccination and an increased incidence of hearing loss compared with the expected incidence in the general population.

O/E Analysis Results

Appendix 7.1 contains the methodology used to calculate and perform the O/E analyses for the AESI. Results of the restricted O/E and sensitivity analysis are presented in Table 145.

Table 145: Sensorineural Hearing Loss w/o Tinnitus, Tinnitus: Restricted O/E and Sensitivity Analysis Results (Cumulative Through 24 August 2022)

	Restricted 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	US (1 to 21)	18 to 59	24.89	0.11	(0.07, 0.16)	0.52	(0.33, 0.76)
	US (1to 14)	18 to 59	20.89	0.13	(0.08, 0.20)	0.65	(0.40, 1.00)
Sensorineural Hearing Loss	EU (1 to 21)	18 to 59	44.68	0.16	(0.12, 0.22)	0.81	(0.59, 1.09)
	EU (1 to 14)	18 to 59	40.76	0.23	(0.16, 0.31)	1.11	(0.80, 1.51)

Key: AESI=Adverse Events of Special Interest; CI=Confidence Interval; EOI=Event(s) of Interest; EU=European Union; LB=Lower Bound; O/E=Observed versus Expected; PE=Point Estimate; PT=Preferred Term; RP=Reporting Percentage; US=United States; W/O=Without

a: Counts included EOI (from valid cases) that occurred within the risk window (Day: 1 to 21, 1 to 14) only.

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

Sensorineural Hearing Loss *w/o Tinnitus*

The EU restricted sensitivity analysis showed an O/E ratio of >1 in the 18 to 59 age group (risk window: 1 to 14 days) only. However, the O/E ratio was not statistically significant (lower bound of 95% confidence interval >1). The O/E ratio was <1 for the US and for the EU over 60 age group in the restricted analysis for both risk windows.

Results of the US and EU O/E analysis (both broad and restricted, where applicable) are provided in Appendix 7.2, this includes cumulative exposure, expected counts and background incidence rates.

Conclusion

Based on the evaluation of the cases and review of safety from other sources, the information is consistent with the information known about SNHL. With the exception of transient tinnitus (listed as an ADR for Ad26.COV2.S) no trends have been identified regarding vestibulocochlear disorders since the launch of the vaccine. The current available evidence is considered insufficient to establish a causal link between the vaccine and SNHL. The Company proposes to monitor this event through routine pharmacovigilance activities.

16.3.6.3.6. Transverse Myelitis

Introduction

Transverse myelitis is listed as an AESI in the cRMP, EU RMP, and the US PVP.

Methods

The Company global safety database was searched for medically confirmed and medically unconfirmed cases received during this reporting period and cumulatively, which coded to the search criteria provided in Appendix 5.

An O/E analysis has been performed and information is presented in the O/E Analysis subsection below.

Results/Discussion

Primary Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 16 (7 medically confirmed and 9 medically unconfirmed), initial, primary dose cases reporting transverse myelitis were identified. All 16 cases were serious and reported a total of 16 serious EOI.

All 16 initial, primary dose cases received during the interval reporting period were reported from post-marketing sources (including spontaneous and solicited cases). No cases were reported from Janssen Sponsored Clinical Studies or Janssen Supported Clinical Studies.

Cumulatively, 112 (75 medically confirmed and 37 medically unconfirmed) primary dose cases reporting transverse myelitis were identified. All 112 cases were serious and reported a total of 127 serious EOI.

Of the 112 cumulative, primary dose cases received, 1 was reported from a Janssen Sponsored Clinical Study, 2 from Janssen Supported Clinical Studies, and 109 from post-marketing sources (including spontaneous and solicited cases).

Janssen Sponsored and Janssen Supported Clinical Studies (Primary Dose Cases)

There were no initial, primary dose cases retrieved from the search of the Company global safety database during the reporting period of 25 February 2022 to 24 August 2022 for either the Janssen Sponsored or Janssen Supported Clinical Studies.

Post-marketing Sources (Including Spontaneous and Solicited) Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 16 post-marketing sources (including spontaneous and solicited), initial, primary dose cases reporting transverse myelitis were retrieved. These 16 post-marketing, initial, primary dose cases reported 16 serious EOI.

Cumulatively, 109 (72 medically confirmed and 37 medically unconfirmed) post-marketing, primary dose cases reporting transverse myelitis were identified. All 109 cases were serious and reported a total of 124 serious EOI.

An overview of these cases is presented in Table 146 below.

Table 146: Characteristics of Post-marketing, Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Transverse Myelitis

Case Characteristics		Number of Cases Received During the Interval Reporting Period=16	Number of Cases Received Cumulatively=109
Sex	Male	9	61
	Female	3	39

Table 146: Characteristics of Post-marketing, Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Transverse Myelitis

Case Characteristics		Number of Cases Received During the Interval Reporting Period=16	Number of Cases Received Cumulatively=109
	NR	4	9
Age (Years)[a]	18 to 35	3	27
Minimum: 25	36 to 50	2	34
Maximum: 67	51 to 64	6	29
Mean: 48.1	≥65	1	6
Median: 52.5	Adult	1	2
	NR	3	11
Sources	Spontaneous	15	108
	Clinical study (noninterventional; solicited)	1	1
Country/Territory[b]	Germany	6	22
	United States	5	58
	Czech Republic	1	1
	Portugal	1	2
	South Africa	1	2
	Spain	1	1
	United Kingdom	1	1
Event Characteristics		**Number of Events=16**	**Number of Events=124**
Seriousness (Event Level)[c]	Serious	16	124
Outcome (Event Level)[c]	Not resolved	9	71
	Resolving	1	19
	Resolved	0	3
	Resolved with sequelae	0	1
	NR	6	30

Key: NR=Not Reported

a: The calculation was based on the current reporting period (25 February 2022 to 24 August 2022). Age group was presented for cases where age was not reported.

b: Countries/Territories were presented in decreasing order for the current reporting period (25 February 2022 to 24 August 2022).

c: Seriousness and outcome have been presented for the events of interest.

Of these 16 post-marketing, initial primary dose cases, the most frequently reported countries/territories of origin (≥5) were Germany (n=6), followed by the US (n=5). These cases concerned 9 males, 3 females, and 4 did not report sex. The age range was from 25 to 67 years.

The frequency distribution of the MedDRA PTs of interest reported in post-marketing, primary dose cases is presented in Table 147 below.

Table 147: Frequency of MedDRA PTs of Interest in Post-marketing, Primary Dose Cases Reporting Transverse Myelitis With the Use of Ad26.COV2.S

MedDRA PTs	Number of Serious Events Reported During the Interval Reporting Period[a]	Number of Serious Events Reported Cumulatively
Myelitis	7	27
Myelitis transverse	7	63
Neuromyelitis optica spectrum disorder	2	7

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: The MedDRA PTs of interest have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022).

The EOI included myelitis, myelitis transverse (n=7 each), and neuromyelitis optica spectrum disorder (n=2). The mean and median TTO were 15 and 14 days, respectively. Where reported (n=10), the outcomes were not resolved (n=9) and resolving (n=1).

Fatal Post-marketing Primary Dose Cases

There were no initial, fatal, post-marketing primary dose cases retrieved from the search of the Company global safety database during the interval reporting period of 25 February 2022 to 24 August 2022.

Booster Dose

During the interval reporting period of 25 February 2022 to 24 August 2022 and cumulatively, 3 (2 medically confirmed and 1 medically unconfirmed) initial cases reported as booster were identified. All 3 cases were serious and reported a total of 3 serious EOI. Of these cases, 2 were heterologous and 1 was homologous.

All 3 cases reported as booster during the interval and cumulatively, were reported from post-marketing spontaneous sources. No cases were reported from Janssen Sponsored Clinical Studies or Janssen Supported Clinical Studies.

A cumulative booster dose CIOMS II LL is presented in Appendix 8.10.

Janssen Sponsored and Janssen Supported Clinical Studies (Booster Dose Cases)

There were no initial cases reported as booster which were retrieved from the search of the Company global safety database during the interval reporting period of 25 February 2022 to 24 August 2022 from either the Janssen Sponsored or Janssen Supported Clinical Studies

Post-marketing Sources (Including Spontaneous and Solicited) Booster Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022 and cumulatively, 3 post-marketing sources (including spontaneous and solicited), initial cases reported as booster were retrieved. These 3 post-marketing, initial, booster dose cases reported 3 serious EOI. The reported countries/territories of origin in these 3 cases reported as booster were [redacted]

[redacted] (n=1 each). All 3 cases concerned females. The age range was from 39 to 67 years.

The EOI included myelitis transverse (n=2) and demyelination (n=1). The mean and median TTO were 80.7 and 101 days, respectively. Where reported (n=2), the outcomes were not resolved and resolved with sequelae (n=1 each).

Fatal Post-marketing Booster Dose Cases

There were no initial, fatal cases reported as booster which were retrieved from the search of the Company global safety database during the interval reporting period of 25 February 2022 to 24 August 2022.

Literature ICSR

ICSR literature cases received during the reporting period of 25 February 2022 to 24 August 2022 were reviewed, and no information was identified that would change the characterisation of risk.

O/E Analysis Results

Appendix 7.1 contains the methodology used to calculate and perform the O/E analysis for the AESI. Results of the restricted O/E and sensitivity analysis are presented in Table 148.

Table 148: Transverse Myelitis: Restricted O/E and Sensitivity Analysis Results (Cumulative Through 24 August 2022)

Restricted 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	33.00	2.06	(1.42, 2.89)	4.11	(2.83, 5.78)
	≥60	8.00	1.42	(0.61, 2.79)	2.83	(1.22, 5.58)
EU	18 to 59	20.92	2.71	(1.68, 4.15)	19.00	(11.75, 29.06)
	≥60	2.08	5.84	(0.75, 20.65)	31.16	(4.01, 110.12)

Key: CI=Confidence Interval; EOI=Event(s) of Interest; EU=European Union; LB=Lower Bound; O/E=Observed versus Expected; PE=Point Estimate; RP=Reporting Percentage; US=United States

a: Counts included EOI (from valid cases) that occurred within the risk window (Day: 1 to 42) only.

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

The restricted sensitivity analysis showed an O/E ratio of >1 in both age groups in both regions. The O/E ratio was statistically significant above 1 (lower bound of 95% confidence interval >1) for all groups.

Results of the US and EU O/E analysis (both broad and restricted, where applicable) are provided in Appendix 7.2, this includes cumulative exposure, expected counts and background incidence rates.

Conclusion

Based on the evaluation of the cases, and review of safety from other sources, the information is consistent with the information known about transverse myelitis. The Company will continue to closely monitor transverse myelitis as an AESI.

16.3.6.4. Vascular Disorders

16.3.6.4.1. Cerebrovascular Events

Introduction

Cerebrovascular events are listed as an AESI in the cRMP, EU RMP, and the US PVP.

During the reporting period of 25 August 2021 to 24 February 2022, 548 cases reporting cerebrovascular events were retrieved from post-marketing sources. The EOI included cerebrovascular accident (n=247), hemiparesis (n=47), and cerebral infarction (n=43). The reported mean and median TTO was 61 days and 22 days, respectively. Comprehensive reviews for cerebrovascular events were repeatedly undertaken in the SSRs including the latest in the bimonthly second and third SSRs submitted, which covered the time frame from 15 January 2022 to 15 May 2022. Overall, the information provided in the SSRs and presented here does not clearly indicate a causal relationship between the vaccine and cerebrovascular events

Methods

The Company global safety database was searched for medically confirmed and medically unconfirmed cases received during this reporting period and cumulatively, which coded to the search criteria provided in Appendix 5.

An O/E analysis has been performed and information is presented in the O/E Analysis subsection below.

Results/Discussion

Primary Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 242 (158 medically confirmed and 84 medically unconfirmed) initial, primary dose cases reporting cerebrovascular events were identified. Of these 242 cases, 240 were serious and 2 were nonserious and reported a total of 288 EOI (285 serious; 3 nonserious).

Of these 242 initial, primary dose cases received during the interval reporting period, 51 were reported from Janssen Sponsored Clinical Studies, 1 from a Janssen Supported Clinical Study, and 190 from post-marketing sources (including spontaneous and solicited).

Cumulatively, 1,693 (1,064 medically confirmed and 629 medically unconfirmed) primary dose cases reporting cerebrovascular events were identified. Of these cases, 1,682 were serious and 11 were nonserious and reported a total of 2,267 EOI (2,252 serious; 15 nonserious).

Of the 1,693 cumulative primary dose cases received, 160 were reported from Janssen Sponsored Clinical Studies, 16 from Janssen Supported Clinical Studies, and 1,517 from post-marketing sources (including spontaneous and solicited cases).

Janssen Sponsored Clinical Studies Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 51 initial, primary dose cases reporting cerebrovascular events were retrieved from Janssen Sponsored Clinical Studies. Of these 51 cases, 40 were from VAC31518COV3001, 9 from VAC31518COV3009, and 1 each from VAC31518COV1001 and VAC31518COV2008. These 51 cases reported 54 EOI (52 serious; 2 nonserious). Of these 51 cases, the most frequently reported countries/territories of origin were the US (n=29), followed by South Africa (n=8) and Brazil (n=6). These cases concerned 28 males and 23 females. The age range was from 46 to 89 years.

The EOI (≥4) included transient ischaemic attack (n=12), ischaemic stroke (n=10), cerebrovascular accident (n=9), and cerebral infarction (n=4). The mean and median TTO were 396.7 and 418 days, respectively. Where reported (n=53), the outcomes were resolved (n=25), resolving (n=10), fatal (n=7), resolved with sequelae (n=6), and not resolved (n=5).

Janssen Supported Clinical Studies Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 1 initial, primary dose case reporting cerebrovascular events was retrieved from a Janssen Supported Clinical Study. This case was from VAC31518COV3021 and concerned an 84-year-old male from South Africa. This case reported a serious EOI of cerebellar infarction. The reported TTO was 6 days, and the event outcome was reported as resolving.

Post-marketing Sources (Including Spontaneous and Solicited) Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 190 post-marketing sources (including spontaneous and solicited), initial, primary dose cases reporting cerebrovascular events were retrieved. These 190, post-marketing, initial, primary dose cases reported 233 EOI (232 serious; 1 nonserious).

Cumulatively, 1,517 (888 medically confirmed and 629 medically unconfirmed) post-marketing, primary dose cases reporting cerebrovascular events were identified. Of these cases, 1,515 were serious and 2 were nonserious and reported a total of 2,078 EOI (2,074 serious; 4 nonserious).

An overview of these cases is presented in Table 149 below.

Table 149: Characteristics of Post-marketing, Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Cerebrovascular Events

Case Characteristics		Number of Cases Received During the Interval Reporting Period=190	Number of Cases Received Cumulatively=1,517
Sex	Male	95	675
	Female	83	788
	NR	12	54
Age (Years)[a]	<18	0	3
Minimum: 20	18 to 35	24	171
Maximum: 90	36 to 50	46	349
Mean: 53	51 to 64	61	467
Median: 53	≥65	42	396
	Neonate	0	2
	Adult	2	4
	Elderly	1	3
	NR	14	122
Sources	Spontaneous	181	1,499
	Clinical study (noninterventional; solicited)	9	18
Country/Territory[b]	United States	77	1,028
	Germany	35	152
	Philippines	26	44
	Poland	9	22
	Italy	7	42
	South Africa	7	12
	France	5	43
	Colombia	3	5
	Greece	3	11
	Ireland	3	6
	Netherlands	3	45
Event Characteristics		**Number of Events=233**	**Number of Events=2,078**
Seriousness (Event Level)[c]	Serious	232	2,074
	Nonserious	1	4
Outcome (Event Level)[c]	Not resolved	62	808
	Resolved	27	260
	Resolving	26	203
	Fatal	21	200
	Resolved with sequelae	8	38
	NR	89	569

Key: NR=Not Reported

a: The calculation was based on the current reporting period (25 February 2022 to 24 August 2022). Age group was presented for cases where age was not reported.

b: Countries/Territories with frequency ≥3 were presented in decreasing order for the current reporting period (25 February 2022 to 24 August 2022).

Table 149: Characteristics of Post-marketing, Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Cerebrovascular Events

Case Characteristics	Number of Cases Received During the Interval Reporting Period=190	Number of Cases Received Cumulatively=1,517

c: Seriousness and outcome have been presented for the events of interest. A single case may report more than 1 event of interest.

Of these 190 post-marketing, initial, primary dose cases, the most frequently reported countries/territories of origin (≥26) were the US (n=77), followed by Germany (n=35) and Philippines (n=26). These cases concerned 95 males, 83 females, and 12 did not report sex. The age range was from 20 to 90 years.

The frequency distribution of the MedDRA PTs of interest reported in post-marketing, primary dose cases is presented in Table 150 below. A single case may contain more than 1 EOI.

Table 150: Frequency of MedDRA PTs of Interest in Post-marketing, Primary Dose Cases Reporting Cerebrovascular Events With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Cerebrovascular accident	62	0	619	0
Cerebral venous sinus thrombosis	24	0	142	0
Hemiparesis[b]	23	0	177	0
Cerebral infarction	17	0	102	0
Transient ischaemic attack	14	0	133	0
Cerebral haemorrhage	12	0	104	0
Ischaemic stroke	9	0	104	0
Cerebral venous thrombosis	8	0	40	0
Hemiplegia[b]	8	0	75	0
Cerebrovascular disorder	5	1	11	2
Cerebral thrombosis	5	0	79	0
Haemorrhagic stroke	5	0	34	0
Hemihypoaesthesia[b]	5	0	8	0

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

a: The MedDRA PTs of interest with a frequency ≥5 have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event of interest.

b: Included MedDRA PTs associated with central nervous system haemorrhages and cerebrovascular accidents. When reported as the only PTs, may not be indicative of central nervous system haemorrhages and cerebrovascular accidents.

The EOI (≥23) included cerebrovascular accident (n=62), cerebral venous sinus thrombosis (n=24), and hemiparesis (n=23). The mean and median TTO were 91.4 and 41 days, respectively. Where reported (n=144), the outcomes were not resolved (n=62), resolved (n=27), resolving (n=26), fatal (n=21), and resolved with sequelae (n=8).

Non-Fatal Cases in Patients ≤ 40 Years of Age

There were a total of 36 non-fatal cases that occurred in patients ≤40 years of age from post-marketing sources. Two of the non-fatal cases involved a haemorrhagic event. Of the 36 non-fatal cases, the EOI was outside the 28-day risk window in 8 cases. Of the remaining 28 cases, 3 were confounded by the patients' medical history and/or concurrent diseases. Of the remaining 25 cases, all lacked relevant details, including TTO, medical history, concomitant medications, and diagnostic test results. Case information for the 36 non-fatal cases that occurred in patients ≤ 40 years of age are included in Appendix 8.11.1.

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 cerebrovascular events being causally associated with Ad26.COV2.S.

Fatal Post-marketing Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 23 post-marketing, initial, primary dose fatal cases with a total of 34 events were retrieved. Of these 23 cases, 17 reported 21 fatal EOI. The fatal EOI (≥2) in the 17 cases were cerebrovascular accident (n=6), cerebral haemorrhage (n=4), ischaemic stroke (n=3), cerebral thrombosis, and hemiparesis (n=2 each).

Of the 17 fatal cases, 13 occurred in patients ≥41 years of age and 4 occurred in patients ≤40 years of age. Of the 13 cases, the EOI was outside the 28-day risk window in 8 cases. Of the remaining 5 cases, 3 were confounded by the patients' medical history and/or concurrent diseases. The remaining 2 cases lacked relevant details, including TTO, medical history, concomitant medications, and diagnostic test results. Case information for the 13 fatal cases that occurred in patients ≥ 41 years of age and detailed information of the 4 cases in patients ≤40 years are included in Appendix 8.11.1.

Booster Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 22 (14 medically confirmed and 8 medically unconfirmed) initial cases reported as booster were identified. Although 1 case was reported as booster, it was determined to be a primary dose case upon further review and has been captured in the primary dose subsection above. All of the remaining 21 (14 medically confirmed and 7 medically unconfirmed) cases were serious and reported a total of 24 EOI (23 serious; 1 nonserious). Of these cases, 11 were heterologous and 10 were homologous.

Of these 21 initial cases reported as booster during the interval, 1 was reported from a Janssen Sponsored Clinical Study and 20 from post-marketing sources (including spontaneous and solicited). No cases were reported from Janssen Supported Clinical Studies.

Cumulatively, 41 (24 medically confirmed and 17 medically unconfirmed) cases reported as booster were identified. All 41 cases were serious and reported a total of 52 EOI (51 serious; 1 nonserious). Of these cases, 27 were homologous and 14 were heterologous.

Of the 41 cumulative booster cases received, 1 was reported from a Janssen Sponsored Clinical Study and 40 from post-marketing sources (including spontaneous and solicited). No cases were reported from Janssen Supported Clinical Studies.

A cumulative booster dose CIOMS II LL is presented in Appendix 8.11.2.

Janssen Sponsored Clinical Studies Booster Dose Cases

During the interval reporting period of 25 February 2022 to 24 August 2022, 1 initial case reported as booster was retrieved from a Janssen Sponsored Clinical Study. This case was from VAC31518COV3001 and concerned a 57-year-old female from [redacted] This serious case reported 1 serious EOI of cerebrovascular accident. The reported TTO was 156 days and the event outcome was reported as resolving.

Janssen Supported Clinical Studies Booster Dose Cases

There were no initial cases reported as booster which were retrieved from the search of the Company global safety database during the interval reporting period of 25 February 2022 to 24 August 2022.

Post-marketing Sources (Including Spontaneous and Solicited) Booster Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 20 post-marketing sources (including spontaneous and solicited), initial cases reported as booster were retrieved. These 20 post-marketing, initial, booster dose cases reported 23 EOI (22 serious; 1 nonserious).

Cumulatively, 40 (23 medically confirmed and 17 medically unconfirmed) post-marketing cases reported as booster were identified. All 40 cases were serious and reported a total of 51 EOI (50 serious; 1 nonserious).

An overview of these post-marketing, booster dose cases is presented in Table 151 below.

Table 151: Characteristics of Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Cerebrovascular Events

Case Characteristics		Number of Cases Received During the Interval Reporting Period=20	Number of Cases Received Cumulatively=40
Sex	Male	11	23
	Female	9	17
Age (Years)[a] **Minimum: 19** **Maximum: 93** **Mean: 50.6** **Median: 49.5**	18 to 35	4	5
	36 to 50	6	10
	51 to 64	5	13
	≥65	5	10
Country/Territory[b]	United States	7	25
	Brazil	4	4
	Germany	4	6
	Philippines	2	2
	Colombia	1	1
	South Africa	1	1
	Spain	1	1
Sources	Spontaneous	18	38
	Clinical study (noninterventional; solicited)	2	2
Classification	Heterologous	11	14
	Homologous	9	26
Event Characteristics		**Number of Events=23**	**Number of Events=51**
Seriousness (Event Level)[c]	Serious	22	50
	Nonserious	1	1
Outcome (Event Level)[c]	Not resolved	6	10
	Fatal	4	7
	Resolved	4	10
	Resolved with sequelae	2	3
	Resolving	1	6
	NR	6	15

Key: NR=Not Reported

a: The calculation was based on the current reporting period (25 February 2022 to 24 August 2022).

b: Countries/Territories were presented in decreasing order for the current reporting period (25 February 2022 to 24 August 2022).

c: Seriousness and outcome have been presented for the events of interest. A single case may report more than 1 event of interest.

Of these 20 post-marketing, initial cases reported as booster, the most frequently reported countries/territories of origin (≥4) were the US (n=7), followed by Brazil and Germany (n=4 each). These cases concerned 11 males and 9 females. The age range was from 19 to 93 years.

The frequency distribution of the MedDRA PTs of interest reported in post-marketing cases reported as booster is presented in Table 152 below. A single case may contain more than 1 EOI.

Table 152: Frequency of MedDRA PTs of Interest in Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Cerebrovascular Events

MedDRA PTs	Number of Serious Events Reported During the Interval Reporting Period[a]	Number of Serious Events Reported Cumulatively
Cerebral thrombosis	2	3
Cerebral venous sinus thrombosis	2	3
Cerebrovascular accident	2	16
Hemiparesis	2	3
Subarachnoid haemorrhage	2	3

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: The MedDRA PTs of interest with a frequency ≥2 have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event of interest.

The EOI (≥2) included cerebral thrombosis, cerebral venous sinus thrombosis, cerebrovascular accident, hemiparesis, and subarachnoid haemorrhage (n=2 each). The mean and median TTO were 98.6 and 48 days, respectively. Where reported (n=17), the outcomes were not resolved (n=6), fatal and resolved (n=4 each), resolved with sequelae (n=2), and resolving (n=1).

Fatal Post-marketing Booster Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 3 initial, fatal cases reported as booster cases with a total of 12 events were retrieved. Of these 3 cases, 2 reported 4 fatal EOI. The fatal EOI in the 2 cases were subarachnoid haemorrhage (n=2), intraventricular haemorrhage (n=1), and intracranial aneurysm (n=1).

Of the 2 fatal cases, 1 occurred in a patient ≥41 years of age and 1 occurred in a patient ≤40 years of age. Both cases were heterologous booster cases. The case that occurred in the patient ≥41 years of age was outside the 28-day risk window and lacked relevant details. The case that occurred in the patient ≤40 years of age is summarised below:

This case (PHIFDA ID: [redacted] concerned a 27-year-old male who experienced intraventricular and subarachnoid haemorrhage with uncal herniation on Day 251 following primary vaccination with Ad26.COV2.S and Day 100 following booster vaccination with the Pfizer BioNTech BNT162b2 COVID-19 vaccine. It was unknown whether the patient had any AEs following primary vaccination. On an unspecified date, the patient was hospitalised, experienced severe headache, vomiting, and generalised body weakness. The cause of death was intraventricular and subarachnoid haemorrhage with uncal herniation. It was unspecified whether an autopsy was performed or not.

MAH Comment: The lack of available information (specifically medical history, concomitant medications, and laboratory and diagnostic test results) precludes a meaningful medical assessment, however, given the long time to onset, a causal link to Ad26.COV2.S is unlikely.

Literature ICSR

ICSR literature cases received during the reporting period of 25 February 2022 to 24 August 2022 were reviewed, and no information was identified that would change the characterisation of risk.

O/E Analysis Results

Cerebrovascular Events - Haemorrhagic

Appendix 7.1 contains the methodology used to calculate and perform the O/E analyses for the AESI. Results of the restricted O/E and sensitivity analysis are presented in Table 153.

Table 153: Cerebrovascular Events - Haemorrhagic: Restricted O/E and Sensitivity Analysis Results (Cumulative Through 24 August 2022)

Restricted 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	Female	18 to 29	9.23	0.35	(0.16, 0.66)	3.06	(1.42, 5.76)
		30 to 39	13.33	0.37	(0.20, 0.64)	4.85	(2.61, 8.24)
		40 to 49	30.37	0.63	(0.43, 0.90)	10.26	(6.94, 14.62)
		50 to 64	59.74	0.42	(0.32, 0.54)	6.83	(5.21, 8.80)
		65 to 74	34.92	0.30	(0.21, 0.42)	3.33	(2.32, 4.63)
		≥75	32.16	0.21	(0.14, 0.30)	2.63	(1.80, 3.70)
	Male	18 to 29	1.61	0.03	(0.00, 0.14)	0.27	(0.02, 1.12)
		30 to 39	9.65	0.17	(0.08, 0.31)	2.02	(0.95, 3.75)
		40 to 49	20.81	0.28	(0.17, 0.43)	4.49	(2.77, 6.88)
		50 to 64	62.73	0.29	(0.22, 0.37)	4.54	(3.49, 5.81)
		65 to 74	31.06	0.20	(0.14, 0.29)	1.84	(1.25, 2.61)
		≥75	21.30	0.16	(0.10, 0.25)	2.22	(1.38, 3.38)
EU	Female	18 to 29	5.27	2.08	(0.70, 4.76)	11.82	(3.98, 27.01)
		30 to 39	2.21	0.61	(0.09, 2.08)	2.55	(0.36, 8.72)
		40 to 49	9.21	0.96	(0.44, 1.81)	2.92	(1.35, 5.50)
		50 to 64	12.82	0.38	(0.20, 0.65)	1.02	(0.54, 1.74)
	Male	18 to 29	6.00	2.04	(0.75, 4.45)	10.67	(3.92, 23.22)
		30 to 39	7.00	0.87	(0.35, 1.79)	2.89	(1.16, 5.95)
		40 to 49	4.00	0.25	(0.07, 0.64)	0.68	(0.19, 1.75)

Key: CI=Confidence Interval; EOI=Event(s) of Interest; EU=European Union; LB=Lower Bound; O/E=Observed versus Expected; PE=Point Estimate; RP=Reporting Percentage; US=United States

a: Counts included EOI (from valid cases) that occurred within the risk window (Day: 1 to 28) only.

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

The US restricted sensitivity analysis showed an O/E ratio of >1 in the US for all female and all male age groups concerned except the male: 18 to 29 age group. Of these, the O/E ratio was statistically significant above 1 (lower bound of 95% confidence interval >1) in all female age groups and in all male age groups except the male 30 to 39 age group.

The EU restricted sensitivity analysis showed an O/E ratio of >1 for all female and all male age groups concerned except the male 40 to 49 age group. Of these, the O/E ratio was statistically significant above 1 (lower bound of 95% confidence interval >1) for the female 18 to 29, 40 to

49 and male 18 to 29 and 30 to 39 age groups. Since the previous PBRER DLP (24 February2022), for the EU female 50 to 64 age group, the restricted sensitivity O/E ratio showed an increase from <1 to >1. The O/E ratio was not statistically significant above 1 (lower bound of 95% confidence interval >1).

Cerebrovascular Events - Non-Haemorrhagic

Results of the restricted analysis with sensitivity analysis are presented in Table 154.

Table 154: Cerebrovascular Events – Non-Haemorrhagic: Restricted O/E and Sensitivity Analysis Results (Cumulative Through 24 August 2022)

Restricted 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	Female	18 to 29	9.44	0.26	(0.12, 0.48)	3.37	(1.57, 6.30)
		30 to 39	17.64	0.21	(0.12, 0.33)	4.33	(2.55, 6.88)
		40 to 49	41.70	0.31	(0.22, 0.42)	7.41	(5.33, 10.03)
		50 to 64	70.43	0.15	(0.12, 0.19)	4.42	(3.45, 5.58)
		65 to 74	38.21	0.09	(0.07, 0.13)	1.28	(0.91, 1.76)
		≥75	50.32	0.09	(0.07, 0.12)	1.17	(0.87, 1.54)
	Male	18 to 29	4.49	0.12	(0.04, 0.30)	1.34	(0.40, 3.26)
		30 to 39	13.52	0.12	(0.07, 0.21)	2.03	(1.10, 3.44)
		40 to 49	19.64	0.11	(0.07, 0.17)	1.94	(1.18, 3.01)
		50 to 64	83.38	0.13	(0.10, 0.16)	2.40	(1.91, 2.97)
		65 to 74	35.93	0.07	(0.05, 0.10)	0.81	(0.57, 1.12)
		≥75	24.24	0.06	(0.04, 0.09)	0.86	(0.55, 1.28)
EU	Female	18 to 29	6.27	0.68	(0.26, 1.46)	2.36	(0.89, 5.06)
		30 to 39	5.21	0.31	(0.10, 0.72)	0.89	(0.30, 2.04)
	Male	18 to 29	8.30	0.8	(0.35, 1.56)	2.74	(1.20, 5.33)
		30 to 39	12.23	0.74	(0.38, 1.28)	2.1	(1.09, 3.64)

Key: CI=Confidence Interval; EOI=Event(s) of Interest; EU=European Union; LB=Lower Bound; O/E=Observed versus Expected; PE=Point Estimate; RP=Reporting Percentage; US=United States

a: Counts included EOI (from valid cases) that occurred within the risk window (Day: 1 to 28) only.

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

The US restricted sensitivity analysis showed an O/E ratio of >1 for all female and all male age groups except the male 65 to 74 and ≥75 age groups. Of these, the O/E ratio was statistically significant above 1 (lower bound of 95% confidence interval >1) for all the female age groups except the 65 to 74 and the ≥75 age groups and for all the male age groups concerned except the 18 to 29 age group.

The EU restricted sensitivity analysis showed an O/E ratio of >1 for the female 18 to 29 and male 18 to 29 and 30 to 39 age groups. Of these, the O/E ratio was statistically significant above 1 (lower bound of 95% confidence interval >1) for the male age groups concerned.

Results of the US and EU O/E analysis (both broad and restricted, where applicable) are provided in Appendix 7.2, this includes cumulative exposure, expected counts and background incidence rates.

Conclusion

Based on the evaluation of the cases, and review of safety from other sources, the information is consistent with the information known about cerebrovascular events. The Company will continue to closely monitor cerebrovascular events as an AESI.

16.3.6.4.2. Disseminated Intravascular Coagulation

Introduction

Disseminated intravascular coagulation (DIC) is listed as an AESI in the cRMP, EU RMP, and the US PVP.

Methods

The Company global safety database was searched for medically confirmed and medically unconfirmed cases received during this reporting period and cumulatively, which coded to the search criteria provided in Appendix 5.

An O/E analysis has been performed and information is presented in the O/E Analysis subsection below.

Results/Discussion

Primary Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 3 (all medically confirmed) initial, primary dose cases reporting DIC were identified. All 3 cases were serious and reported a total of 3 serious EOI.

All 3 initial, primary dose cases received during the interval reporting period were reported from post-marketing spontaneous sources. No cases were reported from Janssen Sponsored Clinical Studies and Janssen Supported Clinical Studies.

Cumulatively, 26 (23 medically confirmed and 3 medically unconfirmed) primary dose cases reporting DIC were identified. All 26 cases were serious and reported a total of 26 serious EOI.

All 26 cumulative, primary dose cases received were reported from post-marketing spontaneous sources. No cases were reported from Janssen Sponsored Clinical Studies or Janssen Supported Clinical Studies.

Janssen Sponsored and Janssen Supported Clinical Studies (Primary Dose Cases)

There were no initial, primary dose cases retrieved from the search of the Company global safety database during the reporting period of 25 February 2022 to 24 August 2022 for either the Janssen Sponsored or Janssen Supported Clinical Studies

Post-marketing Sources (Including Spontaneous and Solicited) Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 3 post-marketing spontaneous sources (including spontaneous and solicited) initial, primary dose cases reporting DIC were retrieved. These 3 post-marketing, initial, primary dose cases reported 3 serious EOI.

Cumulatively, 26 (23 medically confirmed and 3 medically unconfirmed) post-marketing, primary dose cases reporting DIC were identified. All 26 cases were serious and reported a total of 26 serious EOI.

An overview of these cases is presented in Table 155 below.

Table 155: Characteristics of Post-marketing Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Disseminated Intravascular Coagulation

Case Characteristics		Number of Cases Received During the Interval Reporting Period=3	Number of Cases Received Cumulatively=26
Sex	Male	2	13
	Female	1	13
Age (Years)[a]	18 to 35	0	1
Minimum: 40	36 to 50	1	13
Maximum: 40	51 to 64	0	7
Mean: 40	≥65	0	2
Median: 40	NR	2	3
Sources	Spontaneous	3	26
Country/Territory[b]	Netherlands	2	3
	Portugal	1	1
Event Characteristics		**Number of Events=3**	**Number of Events=26**
Seriousness (Event Level)[c]	Serious	3	26
Outcome (Event Level)[c]	Fatal	0	7
	Not resolved	0	6
	Resolving	0	5
	NR	3	8

Key: NR=Not Reported

a: The calculation was based on the current reporting period (25 February 2022 to 24 August 2022). There was only 1 case which reported an age.

b: Countries/Territories were presented in decreasing order for the current reporting period (25 February 2022 to 24 August 2022).

c: Seriousness and outcome have been presented for the events of interest.

All 3 initial, primary dose cases retrieved were literature cases. Two were multiple patient cases from the Netherlands that discussed 3 females and 2 males, respectively with no age reported in either. The third case was a fatal concerning a 40-year-old male from Portugal.

The frequency distribution of the MedDRA PTs of interest reported in post-marketing, primary dose cases is presented in Table 156 below.

Table 156: Frequency of MedDRA PTs of Interest in Post-marketing, Primary Dose Cases Reporting Disseminated Intravascular Coagulation With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Interval Reporting Period		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Disseminated intravascular coagulation	3	0	25	0

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

The EOI included disseminated intravascular coagulation (n=3). The event outcome and TTO were not reported in any of the 3 cases.

Fatal Post-marketing Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 1 post-marketing, initial, primary dose fatal case with no fatal EOI was retrieved.

Booster Dose

There were no initial cases reported as booster which were retrieved from the search of the Company global safety database during the interval reporting period of 25 February 2022 to 24 August 2022. There were no cumulative cases reported as booster.

Literature ICSR

ICSR literature cases received during the reporting period of 25 February 2022 to 24 August 2022 were reviewed, and no information was identified that would change the characterisation of risk.

O/E Analysis Results

Appendix 7.1 contains the methodology used to calculate and perform the O/E analyses for the AESI.

Since the previous PBRER O/E data lock point (24 February 2022), the broad O/E ratio has remained <1 in the US and EU for both age groups. A restricted O/E analysis with sensitivity analysis was therefore not required.

Results of the US and EU O/E analysis (both broad and restricted, where applicable) are provided in Appendix 7.2, this includes cumulative exposure, expected counts and background incidence rates.

Conclusion

Based on the evaluation of the cases, and review of safety from other sources, the information is consistent with the information known about DIC. The Company will continue to closely monitor DIC as an AESI.

16.3.6.5. Hepatic Disorders

16.3.6.5.1. Acute Hepatic Failure

Introduction

Acute hepatic failure is listed as an AESI in the cRMP, EU RMP, and the US PVP.

Methods

The Company global safety database was searched for medically confirmed and medically unconfirmed cases received during this reporting period and cumulatively, which coded to the search criteria provided in Appendix 5.

An O/E analysis has been performed and information is presented in the O/E Analysis subsection below.

Results/Discussion

Primary Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 15 (12 medically confirmed and 3 medically unconfirmed) initial, primary dose cases reporting acute hepatic failure were identified. All 15 cases were serious and reported a total of 21 EOI (19 serious; 2 nonserious).

Of these 15 initial, primary dose cases received during the interval reporting period, 2 were reported from Janssen Sponsored Clinical Studies and 13 from post-marketing spontaneous sources. No cases were reported from Janssen Supported Clinical Studies.

Cumulatively, 95 (51 medically confirmed and 44 medically unconfirmed) primary dose cases reporting acute hepatic failure were identified. Of these cases, 88 were serious and 7 were nonserious and reported a total of 110 EOI (92 serious; 18 nonserious).

Of the 95 cumulative, primary dose cases received, 10 were reported from Janssen Sponsored Clinical Studies, 2 from Janssen Supported Clinical Studies, and 83 from post-marketing spontaneous sources.

Janssen Sponsored Clinical Studies Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 2 initial, primary dose cases reporting acute hepatic failure were retrieved from Janssen Sponsored Clinical Studies. Both cases were from VAC31518COV3001. These 2 cases reported 2 serious EOI. The reported countries/territories of origin were [redacted] and [redacted] (n=1 each). One of these cases concerned a 66-year-old female and the other concerned a 44-year-old male.

The EOI included hepatic cirrhosis (n=2). The mean and median TTO were 379.5 days each, respectively. The reported outcomes were not resolved and resolving (n=1 each).

Janssen Supported Clinical Studies Primary Dose Cases

There were no initial, primary dose cases retrieved from the search of the Company global safety database during the reporting period of 25 February 2022 to 24 August 2022.

Post-marketing Sources (Including Spontaneous and Solicited) Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 13 post-marketing sources (including spontaneous and solicited), initial, primary dose cases reporting acute hepatic failure were retrieved. These 13 post-marketing, initial, primary dose cases reported 19 EOI (17 serious; 2 nonserious).

Cumulatively, 83 (39 medically confirmed and 44 medically unconfirmed) post-marketing, primary dose cases reporting acute hepatic failure were identified. Of these cases, 76 were serious and 7 were nonserious and reported a total of 98 EOI (80 serious; 18 nonserious).

An overview of these cases is presented in Table 157 below.

Table 157: Characteristics of Post-marketing, Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Acute Hepatic Failure

Case Characteristics		Number of Cases Received During the Interval Reporting Period=13	Number of Cases Received Cumulatively=83
Sex	Female	7	44
	Male	6	35
	NR	0	4
Age (Years)[a]	18 to 35	3	13
Minimum: 27	36 to 50	3	13
Maximum: 72	51 to 64	3	25
Mean: 51.8	≥65	4	21
Median: 56	Adult	0	1
	NR	0	10
Sources	Spontaneous	13	83
Country/Territory[b]	United States	5	54
	Philippines	3	4
	Colombia	1	2
	Estonia	1	1
	Germany	1	3
	Poland	1	1
	Portugal	1	1
Event Characteristics		**Number of Events=19**	**Number of Events=98**
Seriousness (Event Level)[c]	Serious	17	80
	Nonserious	2	18
Outcome (Event Level)[c]	Fatal	4	16
	Resolving	4	7
	Not resolved	2	24

Table 157: Characteristics of Post-marketing, Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Acute Hepatic Failure

Case Characteristics		Number of Cases Received During the Interval Reporting Period=13	Number of Cases Received Cumulatively=83
	Resolved	0	12
	NR	9	39

Key: NR=Not Reported
a: The calculation was based on the current reporting period (25 February 2022 to 24 August 2022). Age group was presented for cases where age was not reported.
b: Countries/Territories were presented in decreasing order for the current reporting period (25 February 2022 to 24 August 2022).
c: Seriousness and outcome have been presented for the events of interest. A single case may report more than 1 event of interest.

Of these 13 post-marketing, initial, primary dose cases, the most frequently reported countries/territories of origin (≥3) were the US (n=5), followed by the Philippines (n=3). These cases concerned 7 females and 6 males. The age range was from 27 to 72 years.

The frequency distribution of the MedDRA PTs of interest reported in post-marketing, primary dose cases is presented in Table 158 below. A single case may contain more than 1 EOI.

Table 158: Frequency of MedDRA PTs of Interest in Post-marketing, Primary Dose Cases Reporting Acute Hepatic Failure With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Liver disorder	3	1	5	10
Ascites	3	0	10	0
Hepatic cirrhosis	3	0	11	0
Hepatic failure	2	0	8	0
Hepatic steatosis	1	1	12	7
Acute hepatic failure	1	0	9	0
Drug-induced liver injury	1	0	2	0
Primary biliary cholangitis	1	0	1	0
Regenerative siderotic hepatic nodule	1	0	1	0
Varices oesophageal	1	0	2	0

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: The MedDRA PTs of interest have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event of interest.

The EOI (≥2) included liver disorder (n=4), ascites and hepatic cirrhosis (n=3 each), and hepatic failure and hepatic steatosis (n=2 each). The mean and median TTO were 151.3 and 209 days, respectively. Where reported (n=10), the outcomes were fatal and resolving (n=4 each), and not resolved (n=2).

Fatal Post-marketing Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 4 post-marketing, initial, primary dose fatal cases with 4 fatal EOI were retrieved. The fatal EOI were hepatic failure (n=2), and acute hepatic failure and hepatic cirrhosis (n=1 each).

The first case from Portugal reported from the literature source concerned a male in his 30's with concurrent conditions of obesity and smoking, who experienced severe abdominal pain which occurred 10 days following vaccination with Ad26.COV2.S. The patient was diagnosed with splenic/hepatic failure and a right femoral vein thrombosis. Post-operatively, the patient experienced multi-organ failure and subsequently died 48 hours after admission. An autopsy revealed the cause of death as vaccine induced immune thrombotic thrombocytopenia.

The second fatal case from the US concerned a 56-year-old female with concurrent conditions of hypertension and anxiety, who experienced malaise shortly following vaccination with Ad26.COV2.S and subsequently died due to worsening peripheral neuropathy, an unspecified autoimmune disorder, fall, kidney impairment, liver failure, and status post-implantation of an unspecified medical device. The fatal outcome occurred at an unspecified time following vaccination with Ad26.COV2.S. It was unspecified if an autopsy was performed.

The third fatal case from the US concerned a 71-year-old male with a history of chronic urinary tract infections, diabetes mellitus, and renal stones who experienced fever, vomiting, chills, and was diagnosed with septic shock and thrombosis, approximately 48 hours after vaccination with Ad26.COV2.S. Subsequently, the patient's clinical course worsened, and the patient died 45 days following vaccination with Ad26.COV2.S. The causes of death included fever, septic shock, hepatic failure, hypotension, renal failure, thrombosis, and vomiting. It was unspecified if an autopsy was performed.

The remaining case from the Philippines concerned a 59-year-old male who experienced the following with a fatal outcome: acute respiratory failure, alcoholic liver disease, decompensated hepatic cirrhosis, and upper gastrointestinal bleeding which occurred 344 days following Ad26.COV2.S vaccination. At the time of reporting, it was unspecified if an autopsy was performed.

Booster Dose

There were no initial, cases reported as booster which were retrieved from the search of the Company global safety database during the interval reporting period of 25 February 2022 to 24 August 2022.

Cumulatively, 2 (all medically unconfirmed) cases reported as booster were identified. Of these 2 cases, 1 was serious and 1 nonserious and reported a total of 2 nonserious EOI of liver disorder (n=2). Both cases were homologous.

Both cumulative booster dose cases received were reported from post-marketing sources (including spontaneous and solicited cases). No cases were reported from Janssen Sponsored Clinical Studies or Janssen Supported Clinical Studies.

A cumulative booster dose CIOMS II LL is presented in Appendix 8.12.

Fatal Post-marketing Booster Dose Cases

There were no fatal cases reported as booster which were retrieved from the search of the Company global safety database during the interval reporting period of 25 February 2022 to 24 August 2022.

Literature ICSR

ICSR literature cases received during the reporting period of 25 February 2022 to 24 August 2022 were reviewed, and no information was identified that would change the characterisation of risk.

O/E Analysis Results

Appendix 7.1 contains the methodology used to calculate and perform the O/E analyses for the AESI. Results of the restricted O/E and sensitivity analysis are presented in Table 159.

Table 159: Acute Hepatic Failure: Restricted O/E Analysis with Sensitivity Analysis Results (Cumulative Through 24 August 2022)

	Restricted 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	13.00	4.42	(2.35, 7.56)	8.84	(4.71, 15.11)
	≥60	5.00	4.83	(1.57, 11.27)	9.65	(3.13, 22.53)

Key: CI=Confidence Interval; EOI=Event of Interest; LB=Lower Bound; O/E=Observed versus Expected; PE=Point Estimate; RP=Reporting Percentage; US=United States

a: Counts included EOI (from valid cases) that occurred within the risk window (Day: 1 to 14) only.

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

The US restricted sensitivity analysis showed an O/E ratio of >1 for both age groups. For both age groups, the O/E ratio was statistically significant above 1 (lower bound of 95% confidence interval >1).

Results of the US and EU O/E analysis (both broad and restricted, where applicable) are provided in Appendix 7.2, this includes cumulative exposure, expected counts and background incidence rates.

Conclusion

Based on the evaluation of the cases, and review of safety from other sources, the information is consistent with the information known about acute hepatic failure. The Company will continue to closely monitor acute hepatic failure as an AESI.

16.3.6.6. Renal Disorders

16.3.6.6.1. Acute Kidney Failure

Introduction

Acute kidney failure is listed as an AESI in the cRMP, EU RMP, and the US PVP.

Methods

The Company global safety database was searched for medically confirmed and medically unconfirmed cases received during this reporting period and cumulatively, which coded to the search criteria provided in Appendix 5.

An O/E analysis has been performed and information is presented in the O/E analysis subsection below.

Results/Discussion

Primary Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 26 (20 medically confirmed and 6 medically unconfirmed) initial, primary dose cases reporting acute kidney failure were identified. All 26 cases were serious and reported a total of 30 serious EOI.

Of these 26 initial, primary dose cases received during the interval reporting period, 1 was reported from a Janssen Sponsored Clinical Study and 25 from post-marketing spontaneous sources. No cases were reported from Janssen Supported Clinical Studies.

Cumulatively, 177 (135 medically confirmed and 42 medically unconfirmed) primary dose cases reporting acute kidney failure were identified. All 177 cases were serious and reported a total of 211 EOI (210 serious; 1 nonserious).

Of the 177 cumulative, primary dose cases received, 19 were reported from Janssen Sponsored Clinical Studies, 2 from Janssen Supported Clinical Studies, and 156 from post-marketing sources (including spontaneous and solicited cases).

Janssen Sponsored Clinical Studies Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 1 initial, primary dose case reporting acute kidney failure was retrieved from a Janssen Sponsored Clinical Study. This case was from VAC31518COV3001 and concerned a 58-year-old male from [redacted] who reported a serious EOI of acute kidney injury. The TTO was 179 days and the outcome for the EOI was reported as resolving.

Janssen Supported Clinical Studies Primary Dose Cases

There were no initial, primary dose cases retrieved from the search of the Company global safety database during the reporting period of 25 February 2022 to 24 August 2022.

Post-marketing Sources (Including Spontaneous and Solicited) Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 25 post-marketing sources (including spontaneous and solicited), initial, primary dose cases reporting acute kidney failure were retrieved. These 25 post-marketing, initial, primary dose cases reported 29 serious EOI.

Cumulatively, 156 (114 medically confirmed and 42 medically unconfirmed) post-marketing, primary dose cases reporting acute kidney failure were identified. All 156 cases were serious and reported a total of 190 EOI (189 serious; 1 nonserious).

An overview of these cases is presented in Table 160 below.

Table 160: Characteristics of Post-marketing, Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Acute Kidney Failure

Case Characteristics		Number of Cases Received During the Interval Reporting Period=25	Number of Cases Received Cumulatively=156
Sex	Male	17	88
	Female	6	62
	NR	2	6
Age (Years)[a]	18 to 35	2	9
Minimum: 27	36 to 50	1	18
Maximum: 94	51 to 64	7	54
Mean: 65.4	≥65	14	65
Median: 67.5	Adult	0	1
	Elderly	0	1
	NR	1	8
Sources	Spontaneous	25	155
	Clinical study (noninterventional; solicited)	0	1
Country/Territory[b]	United States	16	115
	Germany	3	7
	Philippines	3	5
	Greece	1	5
	Poland	1	2
	Portugal	1	1
Event Characteristics		**Number of Events=29**	**Number of Events=190**
Seriousness (Event Level)[c]	Serious	29	189
	Nonserious	0	1
Outcome (Event Level)[c]	Fatal	16	63
	Not resolved	3	50
	Resolved	3	25
	Resolving	2	12
	Resolved with sequelae	1	2
	NR	4	38

Table 160: Characteristics of Post-marketing, Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Acute Kidney Failure

Case Characteristics	Number of Cases Received During the Interval Reporting Period=25	Number of Cases Received Cumulatively=156

Key: NR=Not Reported
a: The calculation was based on the current reporting period (25 February 2022 to 24 August 2022). Age group was presented for cases where age was not reported.
b: Countries/Territories were presented in decreasing order for the current reporting period (25 February 2022 to 24 August 2022).
c: Seriousness and outcome have been presented for the events of interest. A single case may report more than 1 event of interest.

Of these 25 post-marketing, initial primary dose cases, the most frequently reported countries/territories of origin (≥3) were the US (n=16), followed by Germany and the Philippines (n=3 each). These cases concerned 17 males, 6 females, and 2 did not report sex. The age range was from 27 to 94 years.

The frequency distribution of the MedDRA PTs of interest reported in post-marketing, primary dose cases is presented in Table 161 below. A single case may contain more than 1 EOI.

Table 161: Frequency of MedDRA PTs of Interest in Post-marketing, Primary Dose Cases Reporting Acute Kidney Failure With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Acute kidney injury	13	0	91	0
Renal impairment	7	0	27	0
Dialysis	3	0	11	0
Renal failure	3	0	30	0
Anuria	1	0	8	0
Azotaemia	1	0	2	0
Haemodialysis	1	0	11	0

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: The MedDRA PTs of interest have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022). A single case may report more than 1 event of interest.

The EOI (≥3) included acute kidney injury (n=13), renal impairment (n=7), and dialysis and renal failure (n=3 each). The mean and median TTO were 129.5 and 87 days, respectively. Where reported (n=25), the outcomes were fatal (n=16), not resolved and resolved (n=3 each), resolving (n=2), and resolved with sequelae (n=1).

Fatal Post-marketing Primary Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 12 post-marketing, initial, primary dose fatal cases reporting 16 fatal EOI were retrieved. The fatal EOI were acute kidney

injury (n=8), dialysis (n=3), renal impairment (n=2), and anuria, azotaemia, and renal failure (n=1 each).

All 12 cases were confounded by medical history or concurrent conditions that included infection (n=7), including bacteraemia, COVID-19 infection, pneumonia, sepsis, and septic shock; diabetes (n=5); chronic kidney disease/end-stage renal disease (n=5); multi-system involvement (n=4); cardiac disease, including CAD/MI (n=2); congestive heart failure (n=2); and hepatic failure (2).

Booster Dose

During the interval reporting period of 25 February 2022 to 24 August 2022, 6 (3 medically confirmed and 3 medically unconfirmed) initial cases reported as booster were identified. All 6 cases were serious and reported a total of 6 serious EOI. Of these cases, 3 were heterologous and 3 were homologous.

All 6 initial cases reported as booster during the interval were from post-marketing spontaneous sources. No cases were reported from Janssen Sponsored Clinical Studies or Janssen Supported Clinical Studies.

Cumulatively, 8 (4 medically confirmed and 4 medically unconfirmed) cases reported as booster were identified. All 8 cases were serious and reported a total of 8 serious EOI. Of these cases, 4 were heterologous and 4 were homologous.

All 8 cumulative, booster dose cases received were reported from post-marketing spontaneous sources. No cases were reported from Janssen Sponsored Clinical Studies or Janssen Supported Clinical Studies.

A cumulative booster dose CIOMS II LL is presented in Appendix 8.13.

Janssen Sponsored and Janssen Supported Clinical Studies (Booster Dose Cases)

There were no initial cases reported as booster which were retrieved from the search of the Company global safety database during the interval reporting period of 25 February 2022 to 24 August 2022 for either the Janssen Sponsored or Janssen Supported Clinical Studies.

Post-marketing Sources (Including Spontaneous and Solicited) Booster Dose Cases

During the reporting period of 25 February 2022 to 24 August 2022, 6 post-marketing sources (including spontaneous and solicited), initial cases reported as booster were retrieved. These 6 post-marketing, initial, booster dose cases reported 6 serious EOI.

Cumulatively, 8 (4 medically confirmed and 4 medically unconfirmed) post-marketing cases reported as booster were identified. All 8 cases were serious and reported a total of 8 serious EOI.

An overview of these cases is presented in Table 162 below.

Table 162: Characteristics of Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Acute Kidney Failure

Case Characteristics		Number of Cases Received During the Interval Reporting Period=6	Number of Cases Received Cumulatively=8
Sex	Male	4	6
	Female	2	2
Age (Years)[a]	<18	1	1
Minimum: 13	36 to 50	0	1
Maximum: 81	51 to 64	0	1
Mean: 54.3	≥65	2	2
Median: 69	NR	3	3
Country/Territory[b]	United States	4	6
	Brazil	1	1
	France	1	1
Sources	Spontaneous	6	8
Classification	Heterologous	3	4
	Homologous	3	4
Event Characteristics		**Number of Events=6**	**Number of Events=8**
Seriousness (Event Level)[c]	Serious	6	8
Outcome (Event Level)[c]	Not resolved	1	3
	NR	5	5

Key: NR=Not Reported

a: The calculation was based on the current reporting period (25 February 2022 to 24 August 2022).

b: Countries/Territories were presented in decreasing order for the current reporting period (25 February 2022 to 24 August 2022).

C Seriousness and outcome have been presented for the events of interest.

Of these 6 post-marketing, initial cases reported as booster, the most frequently reported country/territory of origin (n≥4) was the US (n=4). These cases concerned 4 males and 2 females. The age range was from 13 to 81 years.

The frequency distribution of the MedDRA PTs of interest reported in post-marketing cases reported as booster is presented in Table 163 below.

Table 163: Frequency of MedDRA PTs of Interest in Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Acute Kidney Failure

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious
Acute kidney injury	3	0	4	0
Renal failure	2	0	3	0
Renal impairment	1	0	1	0

Table 163: Frequency of MedDRA PTs of Interest in Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Acute Kidney Failure

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively	
	Serious	Nonserious	Serious	Nonserious

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: The MedDRA PTs of interest have been presented and sorted by decreasing order for the reporting period (25 February 2022 to 24 August 2022).

The EOI included acute kidney injury (n=3), renal failure (n=2), and renal impairment (n=1). The mean and median TTO was 146 and 73.5 days, respectively. Where reported (n=1), the outcome was not resolved (n=1).

Fatal Post-marketing Booster Dose Cases

There were no initial, fatal cases reported as booster which were retrieved from the search of the Company global safety database during the interval reporting period of 25 February 2022 to 24 August 2022.

Literature ICSR

ICSR literature cases received during the reporting period of 25 February 2022 to 24 August 2022 were reviewed, and no information was identified that would change the characterisation of risk.

O/E Analysis Results

Appendix 7.1 contains the methodology used to calculate and perform the O/E analyses for the AESI. Results of the restricted O/E and sensitivity analysis are presented in Table 164.

Table 164: Acute Kidney Failure: Restricted O/E and Sensitivity Analysis Results (Cumulative Through 24 August 2022)

	Restricted 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	19.00	0.48	(0.29, 0.75)	1.03	(0.62, 1.62)

Key: CI=Confidence Interval; EOI=Event(s) of Interest; LB=Lower Bound; O/E=Observed versus Expected; PE=Point Estimate; RP=Reporting Percentage; US=United States
a: Counts included EOI (from valid cases) that occurred within the risk window (Day: 1 to 14) only.
b: Poisson exact confidence interval (95% CI).

The US restricted sensitivity analysis showed an O/E ratio of >1 in the ≥60 age group. The O/E ratio was not statistically significant above 1 (lower bound of 95% confidence interval <1).

Results of the US and EU O/E analysis (both broad and restricted, where applicable) are provided in Appendix 7.2, this includes cumulative exposure, expected counts and background incidence rates.

Conclusion

Based on the evaluation of the cases, and review of safety from other sources, the information is consistent with the information known about acute kidney failure. The Company will continue to closely monitor acute kidney failure as an AESI.

16.3.7. Death

As per PRAC confirmation received in the PRAC FAR (PRAC AR 2022) for the Ad26.COV2.S PBRER (EMEA/H/C/PSUSA/00010916/202202): dated 29 September 2022: a separate death subsection with interval and cumulative death cases is no longer required to be presented in the report body of the current and future PBRERs. However, a separate subsection is found in Appendix 9.9 for those regions requiring this information.

16.4. Characterisation of Risks

The overall current safety profile of the Ad26.COV2.S vaccine was established based on the cumulative spontaneous reports from the Company global safety database on an approximate exposure of 52,684,577 million (CDC [2022], ECDC [2022], KDCA [2022]), available clinical trial data, as well as RWE analyses (see Appendix 9.7). The Company considers, based on the data described in this PBRER, that Ad26.COV2.S vaccine continues to have a positive benefit-risk balance for the active immunisation to prevent COVID-19 infection caused by SARS-COV-2 virus in adults ≥18 years of age.

16.4.1. Characterisation of Important Identified Risks

As endorsed in the PRAC FAR (PRAC AR 2022) for the Ad26.COV2.S PBRER (EMEA/H/C/PSUSA/00010916/202202) received on 29 September 2022), anaphylaxis was removed from the cRMP and will not be presented in future PBRERs.

The cRMP (version 5.0; dated 24 May 2022) was used as a reference for this section. Both VTE and ITP are listed as important potential risks in the current cRMP.

Thrombosis With Thrombocytopenia Syndrome

Potential Mechanisms:

Thrombosis in combination with thrombocytopenia has been reported following vaccination with Ad26.COV2.S. Similar cases of TTS have also been described following administration of other COVID-19 vaccines, particularly with Vaxzevria, which uses a chimpanzee adenovirus (ChAdOx1) vector (Greinacher 2021; Schultz 2021). In literature discussion, this phenomenon is referred to as vaccine-induced immune thrombotic thrombocytopenia (VITT), which is also known, and subsequently referred to in this document as TTS. TTS following vaccination is characterised by the presence of IgG class platelet activating antibodies directed against the cationic platelet chemokine PF4 (CXCL4), subsequently referred to as anti-PF4 antibodies.

A similar phenomenon of thrombosis and thrombocytopenia has also been reported following natural infection by SARS-CoV-2 (Brodard 2021), suggesting a role for the S protein is likely. However, recent studies suggest mechanisms may differ between natural infection and vaccination (Greinacher 2021).

Several hypothetical biological mechanisms have been proposed to explain the pathophysiology of vaccine-associated thromboembolic events with thrombocytopenia. Results from recent mechanistic studies conducted by the Company using clinical trial samples showed no differences in anti-PF4 antibody positivity in thromboembolic cases versus non-thromboembolic controls after vaccination with Ad26.COV2.S or non-COVID-19 Ad26-based Company vaccines. In addition, there was no indication for an increase in the level of pre-existing anti-PF4 antibodies following Ad26.COV2.S vaccination. These data also suggest that the underlying mechanism leading to thromboembolic events and TTS are different, ie, there is no evidence suggesting a general mechanism for coagulation disorders caused by Ad26.COV2.S leading to a spectrum of different thromboembolic events with TTS being the most severe manifestation. To conclude, based on the mechanistic studies (nonclinical studies, and studies using clinical trial samples), the underlying mechanism behind vaccine-associated TTS remains unknown.

With the remaining ongoing additional pharmacovigilance activities, the Company aims to further understand what the potential causes of TTS might be and to gain insights into possible anti-PF4 antibody induction in the context of post-vaccination TTS.

Evidence Source(s) and Strength of Evidence:

Thrombosis in combination with thrombocytopenia, in some cases accompanied by bleeding, has been observed very rarely following vaccination with Ad26.COV2.S. A causal relationship with Ad26.COV2.S is considered plausible. TTS has been reported very rarely with another adenovirus-based COVID-19 vaccine, Vaxzevria. Cases have also been reported following vaccination with mRNA vaccines (Spikevax [Moderna] and Comirnaty [Pfizer-BioNTech]). (Sangli 2021; Al-Maqbali 2021)

The background incidence rate of thrombosis in combination with thrombocytopenia ('combination' defined as thrombocytopenia occurring 10 days before or after thrombosis) was computed as part of the ACCESS project. Cases of thrombosis were categorised into 4 types, including venous thrombosis, arterial thrombosis, venous or arterial thrombosis, and CVST. The incidence rates for all 4 types, in combination with thrombocytopenia, were extremely low, with rates estimated at 1/100,000 person-years (95% CI: 0.70 to 1.43); 1.46/100,000 person-years (95% CI: 1.09 to 1.96); 2.43/100,000 person-years (95% CI: 1.93 to 3.06), and 0.03/100,000 person-years (95% CI: 0.0 to 0.21) for venous, arterial, venous or arterial, and CVST, respectively. These events are likely to be observed in the hospital setting, therefore rates were extracted from a hospitalisation record linkage database, which also includes emergency room visits (ACCESS 2021).

Thrombosis in combination with thrombocytopenia is an ADR described in the CCDS.

Characterisation of the Risk:

While TTS is the AESI, it is a newly identified syndrome that may not have been encoded as such in clinical or post-marketing databases. Various case definitions currently exist (eg, interim BC case definition [Brighton Collaboration 2021], CDC working case definition [Shimabukuro 2021], and the case definition as requested by PRAC, which is based on the case definition as proposed by the UK's NICE [NICE 2020]). For purposes of TTS risk characterisation, all 3 case definitions are used. A broad search was performed to identify cases of TTS in clinical trials and in the post-marketing setting (concomitant SMQ Embolic and thrombotic events, AND HLT Thrombocytopenias OR SMQ Haematopoietic thrombocytopenia). Clinical thromboembolic events were also queried for platelet information reported at any time during the trial. Cases of embolic and thrombotic events in combination with a low platelet count are referred to as 'Qualified for Assessment TTS events'. These Qualified for Assessment TTS events were then reviewed and classified by levels according to the BC level of certainty interim case definitions for TTS (Brighton 2021, including platelet count measurements), to the US CDC working case definition for TTS following COVID-19 vaccination (Shimabukuro 2021), and to the PRAC requested criteria.

An update on the number of cases of TTS from clinical trial and post-marketing experience is provided in Section 16.3.1.1, Thrombosis with thrombocytopenia syndrome of this PBRER.

Risk Factors and Risk Groups:

Although no clear risk factors have been identified, the cases of thrombosis in combination with thrombocytopenia reported in the post-marketing setting more commonly occurred in women aged <50 years.

Preventability:

The CCDS (Section Contraindications) states that Ad26.COV2.S is contraindicated in individuals with a history of confirmed TTS following vaccination with any COVID-19 vaccine. The CCDS (Section Warnings and Precautions) makes reference to this contraindication and states that individuals who have experienced heparin-induced thrombocytopenia should only receive Ad26.COV2.S if the potential benefits outweigh the potential risks. Healthcare professionals should be alert to the signs and symptoms of thromboembolism and/or thrombocytopenia. Those vaccinated should be instructed to seek immediate medical attention if they develop symptoms such as shortness of breath, chest pain, leg pain or swelling, or progressive abdominal pain following vaccination. Additionally, anyone with neurological symptoms including severe or persistent headaches or blurred vision after vaccination, or who experiences spontaneous bleeding, skin bruising (petechia) beyond the site of vaccination after a few days, should seek prompt medical attention. Individuals diagnosed with thrombocytopenia within 3 weeks after vaccination with Ad26.COV2.S should be actively investigated for signs of thrombosis. Similarly, individuals who present with thrombosis within 3 weeks of vaccination should be evaluated for thrombocytopenia.

An initial DHPC has been provided to inform healthcare professionals to facilitate early detection/diagnosis and correct clinical management of thrombosis with thrombocytopenia syndrome. The updated DHPC aims to reinforce the initial messages, in particular with regard to the required specialist clinical management of TTS. In addition, it emphasises potential harms of heparin use for TTS patients and the need to investigate for other TTS symptoms following presentation with post-vaccination thrombosis or thrombocytopenia.

Impact on the Risk-Benefit Balance of the Product:

Thrombosis in combination with thrombocytopenia after vaccination with Ad26.COV2.S is a very rare event which is potentially life-threatening, especially if improperly managed. A causal relationship with Ad26.COV2.S is considered plausible. Adequate risk minimisation that raises public awareness and supports education of healthcare professionals may lead to earlier diagnosis and appropriate treatment, which may improve the prognosis of TTS. Natural infection with SARS-CoV-2 also carries a risk for thrombosis in combination with thrombocytopenia along with other complications (Makowski 2021; Wool 2021). Based on current information, the overall risk-benefit balance for Ad26.COV2.S is considered to remain positive for the indicated target populations.

Public Health Impact:

The occurrence of TTS is very rare following vaccination with Ad26.COV2.S. Therefore, the impact on public health is expected to be low.

Guillain-Barré Syndrome

Potential Mechanisms:

GBS is a rare immune-mediated disorder of the peripheral nerves. Although its cause it not fully understood, the syndrome has been observed to follow viral or bacterial infection with *Campylobacter jejuni*, cytomegalovirus, Epstein-Barr virus, measles, influenza A virus and *Mycoplasma pneumoniae*, enterovirus D68, Zika virus (Esposito 2017). More recently, GBS has been reported in association with SARS-CoV-2 infection (Sheikh 2021) where the absence of autoantibodies suggests a mechanistic pathway other than molecular mimicry typically associated with GBS secondary to infection (Freire 2021).

Since vaccines have an effect on the immune system it is biologically plausible that immunisations may be associated with subsequent GBS (Haber 2009). GBS has been linked in the past with certain vaccines, namely, rabies, polio, and influenza (Stone 2019), as well as hepatitis A and B, MMR-V (IOM 2012), and shingles (FDA 2021). Most recently, cases of GBS have been reported following vaccination with COVID-19 vaccines, including mRNA and adenovirus-based vaccines (Razok 2021; Hasan 2021; Allen 2021). GBS has been reported as a very rare adverse event following immunisation (AEFI) with Ad26.COV2.S. No biological mechanism between GBS and Ad26.COV2.S has been established, although as with other vaccines, immune activation is believed to play a role in the development of the disease.

Evidence Source(s) and Strength of Evidence:

GBS has been observed very rarely following vaccination with Ad26.COV2.S both in clinical trials and in the post-marketing setting. Similar AEs have also been described following administration of other COVID-19 vaccines. Despite no clear biological mechanism being identified, the Company considers the increase in O/E ratios since authorisation to be sufficient evidence for a plausible association between Ad26.COV2.S and GBS.

GBS is an ADR described in the CCDS.

Characterisation of the Risk:

An update on the number of cases of GBS from clinical trial and post-marketing experience is provided in Section 16.3.1.2, Guillain-Barré syndrome of this PBRER.

Risk Factors and Risk Groups:

Based mainly on data from North America and Europe, it has been shown in literature that the GBS incidence increased by 20% for every 10-year increase in age; GBS is usually more frequent in males, with the highest incidence between 50 to 70 years of age (Van Doorn 2020).

Approximately a third of all GBS patients report symptoms of respiratory or gastrointestinal tract infection before the onset of GBS (Van den Berg 2014). Although many different infections have been identified in patients with GBS, case-control studies have revealed associations with only a few pathogens. *Campylobacter jejuni* is the most widely reported infection: it has been found in 25% to 50% of the adult GBS population and is more frequent in Asian countries. Other infections associated with GBS are those due to cytomegalovirus, Epstein–Barr virus, measles, influenza A virus and *Mycoplasma pneumoniae*, as well as enterovirus D68 and Zika virus (Esposito 2017). More recently, GBS has been reported in association with SARS-CoV-2 infection (Sheikh 2021). GBS has been linked in the past with some vaccines, namely, rabies, polio, and influenza (Stone 2019), as well as hepatitis A and B; measles, mumps, rubella and varicella (IOM 2012); and shingles (FDA 2021c). Most recently, cases of GBS have been reported following vaccination with COVID-19 vaccines, including mRNA and adenovirus-based vaccines (Razok 2021; Hasan 2021; Allen 2021).

Preventability:

The CCDS (Section Warnings and Precautions) states that healthcare professionals should be alert of GBS signs and symptoms to ensure correct diagnosis, in order to initiate adequate supportive care and treatment and to rule out other causes.

Impact on the Risk-Benefit Balance of the Product:

Although GBS is a serious event that has been reported following vaccination with Ad26.COV2.S, it has been reported at a very low incidence and adequate risk minimisation via the CCDS is

considered sufficient to manage this risk. Therefore, the impact on the risk-benefit balance for the vaccine is considered to be low.

Public Health Impact:

GBS associated with vaccines typically occurs at a low incidence, resulting in a low public health impact. Although the potential clinical consequences of GBS are serious, this is a risk known to healthcare professionals, with negligible public health impact.

GBS was found to be very rare during Ad26.COV2.S clinical development. Only 3 cases of GBS have been reported to date in clinical trials following Ad26.COV2.S vaccination. Likewise, based on the case reports received from post-marketing experience, the occurrence of GBS following vaccination with Ad26.COV2.S is very rare.

Venous Thromboembolism

Venous thromboembolism has been reclassified as an important identified risk in the EU RMP. The cRMP is in the process of being updated to reflect the reclassification.

Potential Mechanisms:

A potential mechanism for the occurrence of VTE includes a hypercoagulable state due to an excessive pro-inflammatory response to vaccination. Activation of endothelial cells, platelets, and leukocytes with subsequent formation of microparticles can trigger the coagulation system through the induction of tissue factor (Branchford 2018). Vaccination with other viral vaccines such as those against influenza (Christian 2011; Tsai 2005) and human papillomavirus (Scheller 2014) have shown to cause a transient increase in pro-inflammatory cytokine production that may lead to the onset of VTE. This may also translate to other vaccines (Cruz-Tapias 2012; Mendoza-Pinto 2018). An underlying mechanism for VTE without thrombocytopenia has not been confirmed. The presentation of VTE following vaccination with Ad26.COV2.S is in most cases without thrombocytopenia. An underlying mechanism for VTE without thrombocytopenia has not been confirmed. Natural infection with SARS-CoV-2 has shown to be associated with hypercoagulability, pulmonary intravascular coagulation, microangiopathy, and VTE or arterial thrombosis (Ribes 2020).

Recent mechanistic studies (nonclinical studies, and studies using clinical trial samples) conducted by the Company to study the pathogenesis of (vaccine-associated) TTS with potential relevance to VTE, did not provide information on a potential mechanism for vaccine-induced thromboembolic events (including VTE). However, these results suggest that an underlying anti-PF4-based disease spectrum between VTE (without thrombocytopenia) and TTS is unlikely.

Evidence Source(s) and Strength of Evidence:

VTE has been observed rarely following vaccination with Ad26.COV2.S in clinical trials and in the post-marketing setting. While a higher proportion of cases of VTE was observed within the

Ad26.COV2.S group versus the placebo group in trial COV3001, there was no increase in VTE events among individuals who received Ad26.COV2.S in trial COV3009.

Characterisation of the Risk:

An update on the number of cases of VTE from clinical trial and post-marketing experience is provided in Section 16.3.1.3, Venous thromboembolism of this PBRER.

During the reporting period, the Company has updated this risk, and based on the totality of data from both clinical trial and post marketing sources, now considers VTE as an Important Identified Risk for Ad26.COV2.S.

Risk Factors and Risk Groups:

In the general population, important intrinsic factors for the onset of deep vein thrombosis (DVT) and pulmonary embolism include a prior medical or family history of DVT or pulmonary embolism, venous insufficiency, heart disease, obesity, long periods of standing position, and multiparity. Important triggering factors for a DVT/pulmonary embolism event include pregnancy, trauma or a violent effort, deterioration of the general condition, immobilisation, long distance travel, and infection (Samama 2000). On the other hand, CVST, including transverse sinus thrombosis (TST), is a disease more commonly observed in children and young adults. Important risk factors for CVST/TST include thrombophilia, trauma, puerperium, and chronic inflammatory diseases (Stam 2005). In addition, patients with CVST/TST have a strong risk for thrombosis, often misdiagnosed as idiopathic intracranial hypertension (Aldossary 2018).

In trial COV3001, the following underlying risk factors have been identified in participants with VTE: male gender, old age (>65 years), long-haul travel, thrombophilia, obesity, hypertension, and COPD. SARS-CoV-2 infection is also considered an important risk factor, with 46 participants (16 in the Ad26.COV2.S group, 17 in the placebo group, 13 in the cross vaccinated group) having a positive PCR test.

Preventability:

The CCDS (Section Warning and Precautions) provides guidance to healthcare professionals to be alert to the signs and symptoms of thromboembolism.

Impact on the Risk-Benefit Balance of the Product:

VTE is a potentially life-threatening event, and if not recognised or managed appropriately, may result in persistent or significant disability or incapacity, and hence requires immediate medical intervention. VTE has been reported rarely following vaccination with Ad26.COV2.S. In the general population, VTE has an estimated frequency of 100 cases per 100,000 person-years. Adequate risk minimisation via the CCDS is considered sufficient to manage this risk. Based on current information, the overall risk-benefit balance for Ad26.COV2.S is considered to remain positive for the indicated target populations.

Public Health Impact:

Based on the currently available information on the known frequency, clinical characteristics, and outcome of VTE events reported after Ad26.COV2.S vaccination, the public health impact is expected to be low.

16.4.2. Characterisation of Important Potential Risks

Important potential risks that may be associated with the use of Ad26.COV2.S include:

Vaccine-associated Enhanced Disease (VAED), Including Vaccine-associated Enhanced Respiratory Disease (VAERD)

Potential Mechanisms:

Potential mechanisms of enhanced disease may include both T cell-mediated immune responses (a Th2-skewed immune response favouring immunopathology) and antibody-mediated immune responses (antibody responses with insufficient neutralising activity leading to formation of immune complexes and activation of complement or allowing for Fc-mediated increase in viral entry to cells) (Graham 2020).

Evidence Source(s) and Strength of Evidence:

Based on past experiences in the development of vaccines against RSV, Dengue virus, SARS-CoV, and MERS-CoV, there is a theoretical risk for VAED, including VAERD, for SARS-CoV-2 vaccines. As COVID-19 clinical manifestations are not limited to respiratory symptoms, not only VAERD, but also the broader term VAED is being taken into account.

VAERD was first seen in the 1960s in infants with RSV infection after receiving a vaccine against RSV that led to markedly worse respiratory disease as compared to non-vaccinated infants (Chin 1969; Fulginiti 1969; Kapikian 1969; Kim 1969). Subsequently, reports of VAED were reported in individuals without prior exposure to Dengue who received tetravalent Dengue vaccines (Su 2020). Nonclinical experience with SARS-CoV and MERS-CoV based vaccines (Agrawal 2016; Bolles 2011; Deming 2006; Honda-okubo 2015; Houser 2017) also indicated a risk for VAERD, however, this risk could not be confirmed in humans due to the lack of efficacy studies. To date there is no published evidence of VAED in nonclinical studies with IM SARS-CoV-2 vaccines. Furthermore, clinical trials with SARS-CoV-2 vaccines based on technologies other than the Ad26-vector platform, including the large-scale Phase 3 trials that are currently ongoing, have so far not reported any VAED either (Baden 2021; Polack 2020; Voysey 2021).

The observed VAERD in nonclinical studies with SARS-CoV and MERS-CoV based vaccines were attributed to induction of a Th2-skewed immune response. A Th1-skewed immune response as well as the induction of high levels of neutralising antibodies is considered desirable to prevent predisposition to enhanced respiratory disease as observed for RSV vaccines. It has been demonstrated in clinical trials that Ad26-based vaccines do induce humoral and strong cellular responses with a clear Th1 skewing (Anywaine 2019; Barouch 2018; Colby 2020; Milligan 2016;

Mutua 2019; Stephenson 2020; Williams 2020). This type 1 skewing of the immune response is considered to minimise the risk of enhanced disease after SARS-CoV-2 infection.

Studies in Ad26.COV2.S immunised Syrian hamsters and nonhuman primate (NHP) conducted by the Company have shown the absence of enhanced lung pathology, absence of increased viral load, and absence of enhanced clinical signs of disease compared with controls after SARS-CoV-2 inoculation, even under conditions of suboptimal immunity allowing breakthrough infection (van der Lubbe 2021; He 2021). Together with induction of neutralising antibodies and a Th1-skewed immune response after Ad26.COV2.S dosing, these data suggest that the theoretical risk of VAERD and VAED for Ad26.COV2.S is low. These data were corroborated by the findings in clinical trials which have shown no indication of the presence of VAED, including VAERD.

Characterisation of the Risk:

An update on the number of cases of VAED/VAERD from clinical trial and post-marketing experience is provided in Section 16.3.2.1, Vaccine-associated enhanced disease, including vaccine-associated enhanced respiratory disease of this PBRER.

Risk Factors and Risk Groups:

It is postulated that the potential risk may be increased in individuals producing lower neutralising antibody titers or in those demonstrating waning immunity (Graham 2020; Munoz 2020).

Preventability:

An effective vaccine against COVID-19 that produces strong humoral and cellular immune responses with a clear Th1 bias is expected to mitigate the risk of VAED, including VAERD (Lambert 2020; Graham 2020). Such an immune profile is elicited by Ad26.COV2.S in clinical trials and nonclinical studies.

Impact on the Risk-Benefit Balance of the Product:

A confirmed risk of VAED, including VAERD could significantly impact the risk-benefit balance of Ad26.COV2.S. The risk will be further characterised through follow-up of study subjects in Phase 3 trials for the occurrence of severe COVID-19. Within post-authorisation effectiveness studies, the incidence of severe COVID-19 in vaccinated versus non-vaccinated populations will be used as an indirect measure of VAED, including VAERD.

Public Health Impact:

The potential risk of VAED, including VAERD could have a public health impact if large populations of individuals are affected.

Immune thrombocytopenia

Potential Mechanisms:

ITP is an autoimmune bleeding disorder characterised by bleeding due to isolated thrombocytopenia with platelet count less than $100x10^9$ /L (Neunert 2011). Although most cases are asymptomatic, in rare instances ITP may be accompanied by severe bleeding, with cerebral bleeding being 1 of the most severe complications.

The biological mechanism linking Ad26.COV2.S and ITP is not fully known. ITP has been reported in the past with other vaccines, especially live viral vaccines (Di Pietrantonj 2020). ITP has also been described following administration of other COVID-19 vaccines, including mRNA and adenovector-based vaccines (Fueyo-Rodriguez 2021; Welsh 2021; Simpson 2021; Kuter 2021).

Although the exact mechanism of autoimmunity leading to ITP is still unclear, it is assumed that underlying mechanisms for ITP include an alteration of the balance between effector and regulatory immune cells. This imbalance results in a breakdown of the immune tolerance causing increased platelet clearance and impaired thrombopoiesis. Similar to other autoimmune disorders, molecular mimicry with bacterial or viral proteins might be one reason for the pathogenesis of ITP (Marini 2019).

Recent mechanistic studies (nonclinical studies, and studies using clinical trial samples) conducted by the Company to study the pathogenesis of (vaccine-associated) TTS with potential relevance to thrombocytopenia (including ITP), did not provide information on a potential mechanism for vaccine-induced thrombocytopenia (including ITP).

Evidence Source(s) and Strength of Evidence:

Very rare events of serious ITP (including fatal events) have been reported following vaccination with Ad26.COV2.S in clinical trials and in the post-marketing setting. Some of these events occurred in individuals with a history of ITP.

Characterisation of the Risk:

An update on the number of cases of ITP from clinical trial and post-marketing experience is provided in Section 16.3.2.2, Immune thrombocytopenia of this PBRER.

Based on the assessment of the cumulative analysis of cases in preparation for this PBRER, the Company has updated this risk, and based on the totality of data from both clinical trial and post-marketing sources, now considers ITP as an Important Identified Risk for Ad26.COV2.S.

Risk Factors and Risk Groups:

ITP is more common in young and middle-aged female adults, and more common in male children and older male adults (Moulis 2014). Adults are more likely to develop chronic ITP compared to

children (Marini 2019). In patients with ITP, the occurrence of bleeding is strongly inversely correlated with platelet levels, with individuals with $<20x10^9$ /L being at a higher risk for bleeding (Piel-Julian 2018).

Limited data from post-marketing experience, including literature, with Ad26.COV2.S suggest that individuals with chronic or recurrent ITP may be at increased risk of developing ITP following vaccination with Ad26.COV2.S

Preventability:

The CCDS (Section Warnings and Precautions) states that if an individual has a history of ITP, the risk of developing low platelet levels should be considered before vaccination, and platelet monitoring is recommended after vaccination.

Impact on the Risk-Benefit Balance of the Product:

ITP is a potentially life-threatening event, and if not recognised or managed appropriately, may result in persistent or significant disability or incapacity, and hence requires immediate medical intervention. ITP has been reported very rarely following vaccination with Ad26.COV2.S. Based on current clinical trial and post-marketing data and the information in the CCDS, the risk-benefit balance for the vaccine is considered to remain favourable for the indicated target populations.

Public Health Impact:

Based on the currently available information on the known frequency, clinical characteristics, and outcome of ITP events reported after Ad26.COV2.S vaccination, the public health impact is expected to be low.

16.4.3. Description of Missing Information

Use During Pregnancy

Evidence source:

There is very limited experience with the use of Ad26.COV2.S in pregnant women.

Animal data from the EF-PPND toxicity study (TOX14389) with Ad26.COV2.S indicate no AE of Ad26.COV2.S on reproductive performance, fertility, ovarian and uterine examinations, or parturition. In addition, there was no AE of vaccination on foetal body weights, external, visceral and skeletal evaluations, or on post-natal development of the offspring.

At the time of initial cRMP preparation, active vaccination of pregnant women had not been evaluated, as being pregnant or planning to become pregnant was an exclusion criterion in all clinical trials being conducted at that time, with the requirement for use of adequate birth control methods for female participants of childbearing potential. A pregnancy test was systematically being performed in these women before each study vaccine administration.

Safety data with Ad26.COV2.S when administered within 3 months before pregnancy as well as during pregnancy have shown no safety concerns in the mother or child in over 500 reported pregnancies, with over 100 reported pregnancy outcomes. Safety data with other Company Ad26-based vaccines when administered within 3 months before pregnancy as well as during pregnancy have shown no evidence of an increased risk of adverse outcomes in the mother or child in over 2,200 reported pregnancies, with over 1,400 reported pregnancy outcomes.

Based on the nonreplicating nature of the vaccine and on nonclinical and very limited clinical and post-marketing data available to date, including data on the use of other Ad26-based vaccines during pregnancy, the safety profile of Ad26.COV2.S when used in pregnant women is not expected to differ from that in the general population, with no specific safety concerns for pregnant women or foetuses to date. Therefore, as stated in the CCDS (Section Pregnancy, Breastfeeding and Fertility), the administration of Ad26.COV2.S in pregnancy should only be considered when the potential benefits outweigh any potential risks to the mother and foetus.

A Phase 2 trial (COV2004) and a post-authorisation pregnancy exposure registry (COV4005) will assess the safety and immunogenicity of Ad26.COV2.S in pregnant women and their offspring.

An update on the number of cases from clinical trial and post-marketing experience in pregnancy/use in breastfeeding women is provided in Section 16.3.5.1, Use during pregnancy of this PBRER.

Use in Breastfeeding women:

Evidence Source:

At the time of initial c RMP preparation, breastfeeding women were excluded from all clinical trials, except from the Phase 3 trials COV3001 and COV3009. Up to the DLP of 04 October 2021, 239 women who were breastfeeding at baseline have received Ad26.COV2.S in trial COV3001, and 110 women who were breastfeeding at baseline have received Ad26.COV2.S in trial COV3009. No data to assess the safety profile are currently available in this subpopulation and the risk in this population has not yet been defined. Approximately 1,042 breastfeeding women have received Janssen's Ad26-based Ebola vaccine in a clinical trial in Democratic Republic of the Congo. Up to 30 June 2021, there have been 37 cases (post-marketing spontaneous or non-interventional cases) of exposure to Ad26.COV2.S vaccine via breastfeeding. No safety signals were identified. Currently, there is no evidence of SARS-CoV-2 transmission through breast milk. Limited data on breastfeeding women with active SARS-CoV-2 infection showed limited excretion of viral particles but no live virus in breastmilk (Centeno-Tablante 2021). In addition, several reports suggest the presence of secretory IgA against SARS-CoV-2 S protein in breast milk from donors with prior COVID-19 (Fox 2020, Dong 2020; Demers-Mathieu 2020). It is not known whether the components of Ad26.COV2.S or the antibodies induced by Ad26.COV2.S are excreted in human milk. Human data are not available to assess the impact of Ad26.COV2.S on milk production or its effects on the breastfed child.

Anticipated risk/consequence of the missing information

No effects on the breastfed child are anticipated considering results from animal and human studies with Ad26-based vaccines, showing limited dissemination of the vaccine and no replication of the vector following IM injection. In the event that a small quantity of Ad26.COV2.S would be (transiently) excreted via the milk, it would not be considered a risk to the breastfed child, specifically with regard to infections, as Ad26.COV2.S is replication-incompetent and does not encode a complete SARS-CoV-2 virus. Therefore, as stated in the CCDS (Section Pregnancy, Breastfeeding, and Fertility), the administration of Ad26.COV2.S while breastfeeding should be considered when the potential benefits outweigh any potential risks to the mother and child.

Breastfeeding women are being included in trials COV3001 and COV3009 to characterise the safety profile of Ad26.COV2.S in this subpopulation. A small subset of participants within trial COV2004 will be followed up during breastfeeding to assess the transfer of antibodies via breast milk.

Use in Immunocompromised Patients

Evidence source:

Patients with stable and well-controlled medical condition including comorbidities associated with an increased risk of progression to severe COVID-19 (eg, stable/well-controlled HIV infection), or those receiving chronic low-dose (less than 20 mg of prednisone or equivalent) immunosuppressive therapy were not excluded from trials COV3001 and COV3009.

In trial COV3009, 386 subjects who received at least 1 dose of Ad26.COV2.S had a stable/well-controlled HIV infection.

In trial COV3001, 601 (2.7%) subjects in the final analyses set (FAS) and 34 (1.0%) subjects in the safety subset who received Ad26.COV2.S had a stable/well-controlled HIV infection. Subjects with other immunodeficiencies were included at very low numbers, not allowing to provide meaningful data (COV3001 CSR February 2021).

Ad26.COV2.S has not been assessed in immunocompromised individuals including those receiving immunosuppressant therapy. These individuals may have a diminished immune response to Ad26.COV2.S.

Based on the primary analysis results from trial COV3001, no conclusion could currently be made about VE in HIV-infected subjects. In this subpopulation, the number of moderate to severe/critical COVID-19 cases was too small to draw efficacy conclusions but the results did not suggest a negative impact of the vaccine. Additional and longer follow-up time for case accrual data will be gathered as the trial continues to better understand observed data. No clinically relevant difference in the reactogenicity profile could be observed in HIV-infected versus HIV negative subjects.

In the FAS of trial COV3001, SAEs were reported in 4 (0.7%) out of 601 HIV-infected subjects who received Ad26.COV2.S, of which none were considered to be related to the study vaccine by

the investigator. The frequency of reported SAEs was similar in the Ad26.COV2.S and placebo groups.

An update on the number of cases from clinical trial and post-marketing experience in immunocompromised patients is provided in Section 16.3.5.3, Use in immunocompromised patients of this PBRER.

Anticipated risk/consequence of the missing information:

Given the fact that Ad26.COV2.S is a replication-incompetent vaccine, the safety profile of Ad26.COV2.S when used in immunocompromised individuals is not expected to differ from that in the general population, with no specific safety concerns. This was confirmed by clinical trial data with Ad26.ZEBOV, for which the safety and immunogenicity was assessed in HIV-infected adults with infection controlled through antiretroviral therapy. In these trials, there were no specific safety concerns and no notable differences between HIV-infected and healthy subjects with regard to reporting frequency or severity of AEs at any timepoint. The limited safety data available from trial COV3001 are comparable to the findings with Ad26.ZEBOV.

Use in immunocompromised patients will be further characterised in an interventional trial and in the post-authorisation safety studies COV4003 and COV4001 and effectiveness studies COV4004 and COV4002 with Ad26.COV2.S.

Use in Patients With Autoimmune or Inflammatory Disorders

Evidence source:

There is limited information on the safety of Ad26.COV2.S in individuals with autoimmune or inflammatory disorders and a theoretical concern that the vaccine may exacerbate their underlying disease.

Subjects with clinical conditions stable under non-immunomodulator treatment (eg, autoimmune thyroiditis, autoimmune inflammatory rheumatic disease such as rheumatoid arthritis) could be enroled in Phase 3 trials COV3001 and COV3009 at the discretion of the investigator.

An update on the number of cases from clinical trial and post-marketing experience in patients with autoimmune or inflammatory disorders is provided in Section 16.3.5.4, Use in patients with autoimmune or inflammatory disorders of this PBRER.

Population in need of further characterisation:

Use in patients with autoimmune or inflammatory disorders will be further characterised in the post-authorisation safety studies COV4003 and COV4001 with Ad26.COV2.S.

Use in Frail Patients With Comorbidities (eg, Chronic Obstructive Pulmonary Disease [COPD], Diabetes, Chronic Neurological Disease, Cardiovascular Disorders)

Evidence source:

Frail individuals, especially those with multiple comorbidities that may compromise their immune response, are at an increased risk for severe COVID-19. In addition, the safety profile in this subpopulation could vary from that seen in healthy adults. Increased age and comorbidities are the 2 major risk factors for frailty.

Of the 8,936 subjects in the FAS of trial COV3001 who received Ad26.COV2.S and had 1 or more comorbidities, 3,704 (41.5%) were aged ≥60 years, 2,271 (25.4%) were aged ≥65 years, and 495 (5.5%) were aged ≥75 years. The proportion of these subjects that have been determined to be frail is currently unknown (COV3001 CSR February 2021).

There is limited information on the safety of Ad26.COV2.S in frail patients with comorbidities that may compromise their immune response.

Following a protocol amendment for trial COV3001 on 14 December 2020, calculation of a frailty index has been included to be applied to subjects enroled, but these data are not available as part of the primary analysis of this trial.

An update on the number of cases from clinical trial and post-marketing experience in frail patients with comorbidities is provided in Section 16.3.5.5, Use in frail patients with comorbidities (eg, chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders) of this PBRER.

Population in need of further characterisation:

Safety data will be collected in individuals who are frail due to age or debilitating disease in trial COV3001, in the post-authorisation safety studies COV4003 and COV4001 with Ad26.COV2.S, in the post-authorisation effectiveness study COV4002 with Ad26.COV2.S, and through routine pharmacovigilance (PV).

Interaction With Other Vaccines

Evidence source:

As no interaction studies have been performed, there are no data to assess if concomitant administration of Ad26.COV2.S with other vaccines may affect the efficacy or safety of either vaccine.

An update on the number of cases from clinical trial and post-marketing experience in cases with interaction with other vaccines is provided in Section 16.3.5.6, Interactions with other vaccines of this PBRER.

Population in need of further characterisation:

All reports describing interactions of Ad26.COV2.S with other vaccines per national recommendations will be collected and analysed as per routine pharmacovigilance activities. A coadministration study of Ad26.COV2.S with seasonal influenza vaccine (trial COV3005) is ongoing.

Long-term Safety

Evidence source:

There are no available data on the long-term safety of Ad26.COV2.S.

Based on long-term safety data from other Ad26-based vaccines (at least 6 months up to 4.5 years post-vaccination in clinical trials), no long-term safety issues have been identified (Adenoviral Vaccine Safety Database V5.0 2020).

An update on the number of long-term safety cases is provided in Section 16.3.5.7 of this PBRER.

Population in need of further characterisation:

At the time of vaccine availability, the long-term safety of Ad26.COV2.S will not be fully known; however, there are no known risks with a potentially late onset based on the available evidence with other Ad26-based vaccines.

Long-term safety data are being collected for at least 2 years in ongoing trials COV3001 and COV3009 following administration of Ad26.COV2.S, and for up to 1 year in the post-authorisation safety studies COV4003 and COV4001 with Ad26.COV2.S.

Subjects of trials COV3001 and COV3009 who initially received placebo are being unblinded and offered a single dose of Ad26.COV2.S (crossover vaccination), since the vaccine has received an EUA in the US and conditional Marketing Authorisation in the EU/EEA. All subjects will be encouraged to remain in the trial and will be followed for safety as originally planned up to 2 years after vaccination.

16.5. Effectiveness of Risk Minimisation

No significant new information on the effectiveness or limitations of specific risk minimisation activities for the important identified risk or important potential risk has become available during the reporting period for Ad26.COV2.S.

Direct Healthcare Professional Communications have been fully implemented globally and the content related to the risk of TTS is appropriately mitigated through routine risk minimisation measures.

17. BENEFIT EVALUATION

As of 31 July 2022, there have been 574,526,267 confirmed cases of COVID-19 globally, including 6,395,832 deaths. As of 31 July 2022, over 12 billion vaccine doses have been administered. (WHO 2022)

In the US, as of 31 July 2022, there have been a total of 90,626,395 confirmed cases of COVID-19 reported, and 1,009,975 cases of COVID-19 related deaths reported. A total of 603,687,225 vaccine doses have been administered. (CDC 2022)

In the EU/EEA, as of 31 July 2022, there have been a total of 16,12,10,772 confirmed cases of COVID 19 reported, and 11,26,517 cases of COVID 19 related deaths reported. (ECDC 2022b)

Over the course of the SARS-CoV-2 pandemic, changes in SARS-CoV-2 occurred. Some changes may affect the virus's properties, such as how easily it spreads, the associated disease severity, or the performance of vaccines, therapeutic medicines, diagnostic tools, or other public health and social measures. WHO (WHO 2021; CDC 2021a), in collaboration with partners, expert networks, national authorities, institutions and researchers have been monitoring and assessing the evolution of SARS-CoV-2 since January 2020. During late 2020, the emergence of variants in several countries, such as UK, RSA, Brazil, India, US, Peru, Columbia that posed an increased risk to global public health prompted the characterisation of specific VOCs, and VOIs to prioritise global monitoring and research, and ultimately to inform the ongoing response to the COVID-19 pandemic. Current or previous VOCs include Alpha (B.1.1.7, earliest detection: UK), Beta (B.1.351, earliest detection: RSA), Delta (B.1.617.2, earliest detection: India), Gamma (P.1, earliest detection: Brazil) and Omicron (B.1.1.529, earliest detection: South Africa). Current or previous VOIs include Eta (B. 1.525; earliest detection in several countries), Iota (B.1.526, earliest detection: US), Kappa (B. 1.617.1, earliest detection: India), Lambda (C.37, earliest detection: Peru), and Mu (B.1.621, earliest detection: Colombia).

The emergence of SARS-CoV-2 variants with multiple mutations in the S protein have raised concerns because of their increased transmission rates, more severe disease (increased hospitalisations or deaths), and because of the possibility that currently authorised/approved COVID-19 vaccines or otherwise in clinical development will provide reduced protection against these variants (CDC 2021a; Rambaut 2020; Tegally 2020).

17.1. Important Baseline Efficacy/Effectiveness Information

Efficacy data from the primary analysis (cut-off date 22 January 2021) from the ongoing pivotal, randomised, double-blind, placebo-controlled, Phase 3 COV3001 study in adults ≥18 years of age and immunogenicity data to support the efficacy data in study COV3001, from the supporting COV1001, COV1002 and COV2001 studies is provided below.

The efficacy, immunogenicity, and safety data from the COV3001 study supported a favourable benefit-risk profile for Ad26.COV2.S in the proposed indication, ie, active immunisation to prevent COVID-19 caused by SARS-CoV-2 in adults ≥18 years of age. The key efficacy findings are summarised below:

- The co-primary hypothesis testing was successful for both co-primary endpoints and, as such, the ability of a single dose of Ad26.COV2.S at 5×10^{10} vp to protect against moderate to severe/critical COVID-19 as early as 14 days after vaccination was demonstrated in adults ≥18 years of age, including adults ≥60 years of age. The VE (adjusted 95% CI) was 66.9% (59.03; 73.40) and 66.1% (55.01; 74.80) from at least 14 days and at least 28 days after vaccination, respectively.
- Higher VE was observed against severe/critical COVID-19. The VE (adjusted 95% CI) was 76.7% (54.56; 89.09) as of 14 days and 85.4% (54.15; 96.90) as of 28 days after vaccination. This high VE was observed consistently across age groups, countries and regions.
- VE against moderate to severe/critical COVID-19 and against severe/critical COVID-19 after a single dose of Ad26.COV2.S was observed across age groups, countries, and in participants with and without comorbidities, with varying degrees of protection.
- Ad26.COV2.S was observed to have an impact on COVID-19 related hospitalisation (including intensive care unit admission, mechanical ventilation and extracorporeal membrane oxygenation) and COVID-19 associated death. As of 28 days after vaccination, 0 versus 16 COVID-19 related hospitalisations were observed in the Ad26.COV2.S group compared to placebo.
- VE against all severe/critical COVID-19 in US was 78.0% (33.13; 94.58) and 85.9% (-9.38; 99.69), 14 and 28 days after vaccination, respectively. In South Africa this was 73.1% (40.03; 89.36) and 81.7% (46.18; 95.42), respectively and in Brazil this was 81.9% (17.01; 98.05) and 87.6% (7.84; 99.72), respectively, indicating that the vaccine protected against known variants of COVID-19.

17.2. Newly Identified Information on Efficacy/Effectiveness

Although protection with a single dose of Ad26.COV2.S in adults ≥18 years of age, including in adults ≥60 years of age against severe/critical COVID-19, including hospitalisations and deaths related to COVID-19, continued to be observed over time, across age groups, comorbidities, countries/territories, regions, and emerging SARS-CoV-2 variants, including VOCs/VOIs, there was a trend towards a decreased protection against moderate to severe/critical COVID-19 over time. Protection against moderate to severe/critical COVID-19 varied by (newly) emerging SARS-CoV-2 variants, including VOCs/VOIs, throughout the trial, and this potentially contributes to the observed decrease, although waning protection (including waning of immunity) of Ad26.COV2.S cannot be excluded.

Vaccine Efficacy Against Moderate to Severe/Critical COVID-19, Severe/Critical COVID-19 and COVID-19 related Hospitalisations/Deaths

At the time of the final efficacy analysis of the double-blind phase of Study COV3001 evaluating efficacy of a single dose schedule, there was a trend towards a decreased protection against moderate to severe/critical COVID-19 compared to the primary analysis. The estimate of VE against moderate to severe/critical COVID-19 appears higher after boosting with a second dose of Ad26.COV2.S in Study COV3009 than observed with single dose vaccination (COV3001 and COV3009), indicating that a booster dose may be beneficial to increase VE against moderate to severe/critical COVID-19.

Trial VAC31518COV3001

At the final analysis of the double-blind phase, VE (95% CI) of a single dose of Ad26.COV2.S against molecularly confirmed moderate to severe/critical COVID-19 was 56.3% (51.30; 60.84) at least 14 days after vaccination and was 52.9% (47.06; 58.08) at least 28 days after vaccination. Based on the final efficacy analysis of the double-blind phase of Study COV3001, VE (95% CI) against severe/critical COVID-19 was 73.3% (63.94; 80.49) when evaluated at least 14 days after vaccination and 74.6% (64.70; 82.06) when evaluated at least 28 days after vaccination. VE against severe/critical COVID-19 was consistent across age groups, participants without/with comorbidities, regions, countries and against SARS-CoV-2 variants with sufficient cases, including the Beta, Gamma VOCs and Lambda, Mu VOIs (as discussed below). VE estimates (adjusted 95% CI) against severe/critical COVID-19 in the primary analysis were 76.7% (54.56; 89.09) and 85.4% (54.15; 96.90), respectively. VE estimates (adjusted 95% CI) in prevention of COVID-19 related medical intervention (including COVID-19 related hospitalisations linked to objective findings [judged by adjudication committee]) were 76.1% (56.86; 87.67) at least 14 days after vaccination and 75.6% (54.26; 88.00), at least 28 days after vaccination. Ad26.COV2.S also continued to protect against COVID-19 related deaths, with VE estimates (95% CI) of 84.5% (47.30; 97.06) and 82.8% (40.49; 96.77), respectively. All COVID-19- related deaths occurring in the Ad26.COV2.S group were at the time of the primary analysis and in older adults with comorbidities.

When considering the VE against SARS-CoV-2 variants including VOCs/VOIs observed in the study, caution is needed when interpreting data where there were (too) few COVID-19 cases and/or CIs were wide. For the Delta VOC, which emerged late in the study (>5.5 months after vaccination), there were 21 (11 in Ad26.COV2.S group versus 10 in placebo) moderate to severe/critical COVID-19 cases of which 2 cases in each group were severe/critical, precluding meaningful conclusions on VE against this VOC. Similarly, for the Alpha VOC there were 2 versus 4 severe/critical cases in the Ad26.COV2.S group versus the placebo group, not allowing to draw meaningful conclusions for severe COVID 19 caused by this variant. Generally, there was continued protection against severe/critical COVID-19 for SARS-CoV-2 variants, including Beta, Gamma VOCs (64%, 78%), Lambda, Mu VOIs (67%, 80%).

Differences were observed in protection against moderate to severe/critical COVID 19 among the SARS-CoV-2 variants including VOCs/VOIs (range VE estimates 10%-70%). No reduction in VE estimates compared to that of the reference strain (VE estimate [95% CI] 58.2% [34.96; 73.72] at least 28 days after vaccination) for the Alpha VOC and other variants, while the VE estimates for the Delta, Gamma VOCs, Mu, Lambda VOIs were reduced (<36%). The VE estimate (95% CI) for the Beta VOC, at least 28 days after vaccination was 51.9% (19.06; 72.19). These findings potentially contribute to the observed reduction in protection against moderate to severe/critical COVID-19 since the primary analysis, however waning protection cannot be excluded.

While the analyses of Delta cases from clinical studies remained inconclusive, multiple sources of evidence confirm vaccine effectiveness against observed COVID-19 and COVID-19-related hospitalisation related to the Delta VOC in a real world setting.

Trial VAC31518COV3009

Efficacy results from the primary analysis of ongoing Phase 3 Trial VAC31518COV3009, in which an Ad26.COV2.S booster dose is administered 2 months after the first vaccination, suggest that protection against moderate to severe/critical COVID-19 (including against SARS-CoV-2 VOC) and severe/critical COVID-19 increases. At the primary analysis, VE (adjusted 95% CI) against moderate to severe/critical COVID-19 (primary endpoint) was 75.2% (54.55;87.30) when evaluated at least 14 days after second vaccination. VE against moderate to severe/critical COVID-19, when evaluated at least 14 days after boosting, was consistent among age groups as well as among participants with and without comorbidities. Some regional differences in VE were observed: in the US, VE (95% CI) against moderate to severe/critical COVID-19 was 93.7% (58.45;99.85) while lower VE (60.0% to 68.8%) was observed in other regions, which was possibly driven by reduced VE against certain SARS-CoV-2 variants. Final analysis results of variants with sufficient cases available for meaningful interpretations (Alpha [B.1.1.7] and Mu [B.1.621]) show that, after the first dose of JCOVDEN, efficacy 14 days post-dose 1 (Day 15-Day 56) for these 2 variants was 73.2% [95% CI: 48.4; 87.1] and 38.6% [95% CI: -43.9; 75.1], respectively. After the second dose (≥71 days), efficacy for Alpha and Mu was 83.7% [95% CI: 43.8; 97.0] and 53.9% [95% CI: -48.0; 87.6], respectively. Statistically significant efficacy for Mu and Delta (4 and 3 Delta cases in the JCOVDEN group and placebo group, respectively) was not demonstrated. There were no reference strain cases in either the JCOVDEN or placebo group in the follow-up 14 days after the booster dose (≥71 days). Note that single dose VE estimates in study COV3009 from Day 15 to Day 56 were similar to those observed in the primary analysis of COV3001 with a similar follow-up time, despite the fact that the studies were not conducted at the same time and in partially different locations.

Altogether, the totality of data allows us to conclude that vaccination with Ad26.COV2.S remains efficacious against severe/critical COVID-19, including hospitalisations and deaths related to COVID-19, including against some variants. While the analysis of Delta cases from clinical trials remains inconclusive, multiple sources of evidence confirm vaccine effectiveness against observed COVID-19 and COVID-19-related hospitalisation related to the Delta VOC in a real world setting.

In addition to these clinical efficacy studies, the Company has conducted a review during the renewal reporting period of the currently available RWE effectiveness data on Ad26.COV2.S. The review included Company-sponsored, collaborative, and publicly available RWE studies reporting on the vaccine effectiveness of Ad26.COV2.S and is summarised below.

Trial VAC31518COV4002

Interim results (up to 183 days after vaccination; median follow-up of 129 days) are available from Study COV4002, which is an observational, longitudinal, post-authorisation study to assess the effectiveness of a single dose of Ad26.COV2.S (5×10^{10} vp) in clinical practice, with onset 14 days after vaccination, in adults ≥18 years of age in the US. HealthVerity COVID-19 data consists of longitudinal, de-identified patient-level real world data for approximately 160M patient lives submitted by US providers of inpatient, outpatient, pharmacy, and laboratory services from

01 March 2021 to 31 August 2021 from open-source medical claims data aggregated by HealthVerity. Overall, the results of the interim analysis indicate that a single dose of Ad26.COV2.S protects against observed COVID-19 and COVID-19-related hospitalisation in the real world setting and that the VE observed in pivotal study COV3001 translates into clinical practice, with sustained effectiveness up to 183 days post-vaccination (median 129 days for observed COVID-19 and 130 days for COVID-19 related hospitalisation), including amid high Delta variant incidence.

Study VAC31518COV3012 (Sisonke [Together])

Sisonke is a Phase 3B, open-label, implementation study of VE of Ad26.COV2.S in HCW sponsored by the South African Medical Research Council in South Africa which commenced on 17 February 2021 and ended on 16 May 2021 (Bekker 2021). This study focused on HCWs aged >18 years of age with SARS-CoV-2 test results collected by the National Institute for Communicable Diseases in the COVID-19 notifiable medical conditions sentinel surveillance system. While not explicitly deriving VE against infection and hospitalisation, differences were noted between Beta and Delta breakthrough infection patterns in SISONKE HCWs, with Delta producing a higher proportion of hospitalisations in individuals between 31 to 54 years of age (60%) than Beta (51%) (Goga 2021). Although a higher proportion of HCWs required general ward care during the Delta period compared to the Beta period (89% and 78%, respectively), fewer HCWs required high or intensive care (4% and 7% during Delta compared to 7% and 16% during Beta).

Results of additional RWE studies that report Ad.26.COV2S effectiveness have recently been reported. These studies investigated the RWE of Ad26.COV2.S for prevention of COVID-19, hospitalisation and death using electronic health records from multi-state health systems, networks, and hospitals. These studies focus on individuals who received a single dose of the Ad26.COV2.S vaccine with comparison to control groups following local regulatory approval. Results were reported across different geographies, age categories, ambulatory, and inpatient care settings. In some reports, comparative effectiveness of Janssen, Moderna and Pfizer-BioNTech vaccines were reported on; however, this summary focuses on the VE of Ad26.COV2.S. Despite these limitations, results from many of the studies (Bekker 2021; Corchado-Garcia 2021; Moline 2021; de Gier 2021) are consistent with the vaccine effectiveness seen with the single dose Ad26.COV2.S vaccine in COV4002.

Key Immunogenicity Data

Data from the primary analysis of COV2008 Cohort 1 have demonstrated NI of neutralising antibody titers and response rates against the reference strain and the Delta variant after Ad26.COV2.S homologous booster vaccination at ≥6 months, compared with primary vaccination with Ad26.COV2.S. An exploratory descriptive analysis showed that neutralising antibody titers and response rates against the Beta variant at Day 15 post-homologous booster are consistent with non-inferiority criteria compared to neutralising antibody titers and response rates at Day 29 after primary vaccination. Titers and response rates against the reference strain, Delta, and Beta variants post-homologous booster were generally maintained between Day 15 and Day 29. Considering

that neutralising antibody titers correlate with VE (Khoury 2021; Fong 2022), this demonstration of NI links the immunogenicity data following the booster to the efficacy demonstrated in the randomised controlled study (COV3001) following the primary vaccination. In addition, non-powered descriptive analyses indicate that neutralising antibody titers following a boost were superior compared to those following primary vaccination, in line with the higher efficacy estimates observed in the COV3009 efficacy study. These data are consistent with the previously submitted results from COV1001 Cohort 2a and confirm that a higher immune response was observed with an interval of at least 6 months between the primary vaccination and the booster dose compared with shorter intervals.

Likewise, in COV2008 Cohort 2, NI was also demonstrated against the reference strain and the Delta variant after Ad26.COV2.S heterologous booster vaccination at ≥6 months, compared with primary vaccination with Pfizer BNT162b2. Neutralising antibody GMTs and seropositivity rates were also significantly increased against the Beta variant. Titers and responder rates post heterologous booster increased substantially between Day 15 and Day 29 for the reference strain and the Beta and Delta variants, at all dose levels. These data are consistent with previously submitted interim data (binding and neutralising antibodies) on heterologous boosting with Ad26.COV2.S from the Mix and Match Study DMID 21-0012.

Neutralising antibody responses against the Omicron variant were lower than those against the reference strain, Delta variant, and Beta variant after homologous or heterologous booster vaccination with Ad26.COV2.S at the 5×10^{10}vp dose level. However, the kinetics of the neutralising antibodies against the Omicron variant were similar to neutralising antibodies against the other strains. By Day 29 post-homologous booster, neutralising antibody titers were maintained at Day 15 levels, while titers and responder rates post heterologous booster increased between Day 15 and Day 29. Non-powered descriptive analyses indicate that by Day 15, neutralising antibody titers and response rates against the Omicron variant post-homologous booster at the 5×10^{10}vp dose level were superior to those observed post primary vaccination.

Heterologous boosting with Ad26.COV2.S is further supported by additional results from Mix and Match Study DMID 21-0012 and Study COV-BOOST, in which a heterologous Ad26.COV2.S was administered following completion of primary vaccination with an mRNA or adenoviral vector based COVID-19 vaccine. In addition, given the high number of people who were vaccinated with an inactivated whole-virion COVID-19 vaccine (CoronaVac) globally, immunogenicity data from Study RRH-001 on the evaluation of heterologous boosting with Ad26.COV2.S after primary vaccination with an inactivated whole-virion COVID-19 vaccine was included as well. Overall, heterologous boosting with Ad26.COV2.S following any of the abovementioned primary vaccination regimens strongly increased neutralising and binding antibody responses as well as cellular responses, including against some SARS-CoV--2 variants (including Beta, Delta, and Omicron).

Finally, homologous and heterologous boosting with Ad26.COV2.S are further supported by data from the literature. Fully vaccinated individuals with one of the 3 priming regimens (Ad26.COV2.S, mRNA-1273, or BNT162b2), who received a boost with one of these

3 vaccines in any combination, showed an increase in neutralising/binding antibody and cellular responses to the SARS-CoV-2 reference strain and several variants including Beta, Delta, and Omicron, compared with pre-boost timepoint. This translates into an increased vaccine effectiveness against COVID-19-related infections, hospitalisations, and deaths after Ad26.COV2.S boosting, including during the Omicron-emerging and Omicron-predominant periods, as shown in RWE studies.

17.3. CHARACTERISATION OF BENEFITS

With the disease burden of COVID-19 remaining high, a COVID-19 vaccine that can easily be administered in a regimen that elicits long-term high protection against symptomatic COVID-19 is needed. Protection against severe/critical disease and in older/fragile age groups and other populations at high risk will reduce the burden on health care systems by lowering COVID-19 related hospitalisations/deaths. Also, protection with a similar magnitude against existing and (newly) emerging SARS-CoV-2 variants, will be of high value to continue fighting the COVID-19 pandemic.

18. INTEGRATED BENEFIT-RISK ANALYSIS FOR APPROVED INDICATIONS

18.1. Benefit-Risk Context – Medical Need and Important Alternatives

Medical Need

On 11 March 2020, the WHO characterised the COVID-19 outbreak as a pandemic. In response to the public health emergency, the EMA pandemic Task Force was formed from 31 March 2020 (EMA 2020a). The Ad26.COV2.S prophylactic vaccine programme is an accelerated development programme that was designed specifically to address the COVID-19 pandemic. Despite the present availability of currently authorised vaccines, and the prevalence of natural infections, herd immunity has not yet been achieved, and travel from countries with a higher incidence of infection as well as the emergence of new variants means that the potential for new outbreaks is still a significant concern. The risk of outbreaks and emergence of new variants highlights the need to continue primary vaccination. A 1-dose regimen and favourable storage conditions are advantages conferred by the Ad26.COV2.S vaccine in protecting against COVID-19 infection caused by the SARS-CoV-2 virus, which are particularly important for immunising hard-to-reach populations.

Over the course of the SARS-CoV-2 pandemic, several new SARS-CoV-2 VOCs emerged in the UK (B.1.1.7 lineage [alpha]), in Brazil (P.1 lineage [gamma]), in the Republic of South Africa (B.1.351 lineage [beta], B.1.1.529 lineage [omicron]), and in India (B.1.617 lineage [Delta]), and new VOIs (eg, B.1.427/B.1.429 lineage [CAL.20, epsilon] in California) continue to emerge, which may spread globally. The emergence of SARS-CoV-2 variants with multiple mutations in the S protein have raised concerns because of their increased transmission rates, more severe disease (increased hospitalisations or deaths), and because of the possibility that current currently authorised/approved COVID-19 vaccines or otherwise in clinical development will provide reduced protection against these variants (CDC 2021b, Rambaut 2020, Tegally 2020). For example, data suggest that the B.1.351 variant is not

neutralised by some monoclonal antibodies directed to the SARS-CoV-2 S protein and is resistant to neutralisation by plasma from individuals previously infected with 'Wuhan-like' SARS-CoV-2 (Wibmer 2021), although data obtained to date suggest that the impact on neutralisation by convalescent and post-vaccination sera is minimal to moderate (CDC 2021c). As of 31 July 2022, there have been 574,526,267 confirmed cases of COVID-19, including 6,395,832 deaths worldwide (WHO 2022). In the EU/EEA, as of 31 July 2022, there have been a total of 16,12,10,772 confirmed cases of COVID-19 reported, and 11,26,517 cases of COVID-19 related deaths reported (ECDC 2022b).

SARS-CoV-2 can cause widespread damage in different organ systems mediated by the host's immune response. Severity of illness can range from asymptomatic infection to severe multiorgan failure. The incubation period following exposure to SARS-CoV-2 has been estimated anywhere between 2 and 14 days, and varies by VOCs. In a pooled analysis of 181 confirmed COVID-19 cases from China the median incubation period was estimated to be 5.1 days (95% confidence interval, 4.5 to 5.8 days). Noteworthy, compared with earlier VOCs, shorter incubation periods have been documented in infections with Delta and Omicron variants, with a median incubation period of 4 days. (Hernandez Acosta 2022)

COVID-19 is associated with a severe disease course in about 23% and mortality in about 6% of infected persons. Individuals with comorbidities and clinical features associated with severity should be monitored closely, and preventive efforts should especially target those with diabetes, malignancy, and immunosuppression (Li 2021). A recent epidemiological update by WHO reported that more than 200 countries around the world have reported SARS-Co-V-2 variants of concern of which the newer VOC, Omicron has been reported by 76 countries so far since first being reported in November 2021. However, the case fatality rate is affected by factors that include age, underlying preexisting conditions, and severity of illness and significantly varies between countries (Cascella 2022). Therefore, while the understanding of the epidemiology and clinical spectrum of COVID-19 is still evolving, the disease burden continues mounting.

18.2. Benefit-risk Analysis Evaluation

Key Benefits

The SARS-CoV-2 outbreak constitutes a public health emergency of international concern. The ongoing COVID-19 pandemic has already caused over 6 million deaths worldwide and continues to devastate lives. Effective and safe COVID-19 vaccines that can be easily administered are pivotal in ending this pandemic. Therefore, the MAH has evaluated efficacy, immunogenicity, and safety of a 1-dose COVID-19 vaccine, Ad26.COV2.S, in an ethnically and geographically diverse adult population.

Key Efficacy Data From Phase 3 Studies and RWE

Previously submitted results from single dose study COV3001 and homologous booster study COV3009 indicated that administration of a homologous booster 2 months after primary vaccination with Ad26.COV2.S increased the point estimates of VE against symptomatic and

severe/critical COVID-19, including against SARS-CoV-2 variants with sufficient cases for analysis, based on a 1-month median follow-up after the booster vaccination.

Efficacy data from these Phase 3 studies have shown that vaccination with Ad26.COV2.S also shows a level of protection against any SARS-CoV-2 infections (both symptomatic and asymptomatic infections combined), with higher VE point estimates after a homologous booster. Although VE (95% CI) against asymptomatic SARS-CoV-2 infections was generally low after single dose vaccination in COV3001 (28.9% [19.99; 36.78]), a country specific subgroup analysis for the US has shown a VE (95% CI) of 58.8% (44.69; 69.54) when evaluated at least 28 days after vaccination, confirming that VE always needs to be interpreted in view of emerging SARS-CoV-2 variants, including VOCs/VOIs, with varying levels protection against these. Furthermore, in case of breakthrough infections, a reduction in severity, duration, and symptoms of COVID-19 and a reduction in viral load was observed, potentially reducing the risk of transmission. This shift to lower COVID-19 severity may additionally explain the generally low VE estimates against asymptomatic SARS-CoV-2 infections compared with the higher VE estimates against more severe COVID-19.

Furthermore, recently published data from SISONKE 2 and other RWE studies confirm the benefit of a homologous or heterologous Ad26.COV2.S booster dose in protecting against COVID-19 related infections, hospitalisations, and deaths, also during the Omicron-emerging and Omicron predominant periods.

Supporting Immunogenicity Data

Previously submitted results from studies COV1001, COV1002, COV2001, and COV3009 have shown that a homologous booster dose of Ad26.COV2.S (5×10^{10} vp), either 2 or 3 months after the first vaccination, induced an increase in humoral immune responses, which were durable up to at least 4 to 6 months after booster vaccination. These data are consistent with the homologous Ad26.COV2.S booster data from the Mix and Match Study DMID 21-0012, in which the booster was administered >12 weeks after primary vaccination. In addition, a homologous Ad26.COV2.S booster, administered 2 or 3 months after primary vaccination in adults ≥18 years of age, elicited cellular responses that persisted up to at least 6 months after boosting. These data further support the durability of the immune responses elicited by a homologous Ad26.COV2.S booster.

Data from the primary analysis of COV2008 Cohort 1 have demonstrated NI of neutralising antibody titers and response rates against the reference strain and the Delta variant Ad26.COV2.S homologous booster vaccination at 6 months, compared with primary vaccination with Ad26.COV2.S in COV2008 Cohort 2, NI was also demonstrated against the reference strain and the Delta variant after Ad26.COV2.S heterologous booster vaccination at ≥6 months compared with primary vaccination with Pfizer BNT162b2. Neutralising antibody responses against the Omicron variant were lower than those against the reference strain, Delta variant, and Beta variant vaccination with Ad26.COV2.S at the 5×10^{10}vp dose level. However, the kinetics of the neutralising antibodies against the Omicron variant were similar to neutralising antibodies against the other strains. Heterologous boosting with Ad26.COV2.S was further supported by data from DMID 21-0012, COV-BOOST, RRH-001 and by data from the literature.

Overall Assessment of Benefit

Ad26.COV2.S is efficacious, elicits a durable humoral and cellular immune response, has favourable storage conditions, and only requires administration of a single dose for primary immunisation, which simplifies deployment of the vaccine. Both antibody levels and VE increased after the administration of a homologous Ad26.COV2.S booster 2 months after primary vaccination, supporting the hypothesis that antibody levels correlate with protection. For the reference strain and Delta, Beta, and Omicron variants, heterologous booster vaccination with Ad26.COV2.S elicited higher neutralising antibody titers than homologous booster vaccination at all dose levels evaluated. Homologous and heterologous booster vaccination with Ad26.COV2S at the 5×10^{10} vp level and as low as 1×10^{10} vp given ≥6 months after primary vaccination induced neutralising antibody levels that were observationally higher than those seen following a homologous booster at 2 months. Together, these data indicate that a heterologous booster at the 5×10^{10} vp dose level, but also potentially at lower dose levels, will result in levels of protection that are at least as high as for a homologous boost 2 months after primary vaccination.

The long-term and robust platform data demonstrate durable immune responses for the Ad26-based vaccines. Therefore, Ad26.COV2.S remains a valuable and relevant asset to address the COVID-19 pandemic. Ad26.COV2.S is approved in the EU for use as a booster vaccine as it has been demonstrated to be effective for both homologous and heterologous booster vaccination. In low- and middle-income countries there is still a high need for both primary and booster vaccination and EMA licence is key as many of these countries have a reliance mechanism in place.

The safety concerns from the EU RMP (version 4.2, dated 12 July 2022) in place at the end of the renewal reporting period are presented in Section 16.1.2, Summary of Safety Concerns at the End of the Reporting Period.

Key Risks

The safety concerns from the current cRMP (version 5.0; dated 24 May 2022) are provided below:

Safety Concerns at the End of the PBRER Reporting Period[a]

Important Identified Risks	Thrombosis with thrombocytopenia syndrome Guillain-Barré syndrome
Important Potential Risks	Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) Venous thromboembolism[b] Immune thrombocytopenia[c]
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

Key: cRMP=Core Risk Management Plan; ITP=Immune thrombocytopenia

Safety Concerns at the End of the PBRER Reporting Period[a]

a: During the reporting period, Anaphylaxis was removed from the list of safety concerns.
b: Venous thromboembolism has been reclassified as an important identified risk. The cRMP is in the process of being updated to reflect the reclassification.
c: ITP is comparable to thrombocytopenia, including ITP in the European Risk Management Plan.

Overall Assessment of Risk

The initial safety profile of Ad26.COV2.S vaccine was established at the time of first authorisation (at the start of the renewal reporting period) based on the interim analysis from the pivotal Phase 3 Ad26.COV2.S efficacy and safety study COV3001, complemented by blinded safety data from then ongoing Phase 1/2 and 3 studies. Since then, additional information became available through routine safety PV activities (such as signal detection) for which the results were reflected in updates of the RMP, the Monthly Summary Safety Reports, and amendments to the CCDS.

A single dose of Ad26.COV2.S has an acceptable safety and reactogenicity profile in adults ≥18 years of age, including adults ≥60 years of age. In general, lower reactogenicity was observed in older adults compared to younger adults. The most frequently reported solicited (local and systemic) AEs (collected up to 7 days after vaccination in the Safety Subset) after a single dose of Ad26.COV2.S 5×10^{10} vp were vaccination site pain, fatigue, headache, and myalgia. Most AEs were of mild or moderate severity, were transient in nature and generally resolved within 1 to 2 days post-vaccination.

The most frequently reported unsolicited AEs (collected up to 28 days after vaccination in the Safety Subset) were headache, fatigue, myalgia, and vaccination site pain, which were also recorded as solicited AEs. The most frequently reported unsolicited AEs by PT, not recorded as solicited AEs, were chills, nasal congestion, arthralgia, cough, and diarrhoea. Most were of mild or moderate severity, and most were considered not related to the study vaccine by the investigator. The overall frequency of SAEs was low and balanced between placebo and active groups.

Post-marketing experience with Ad26.COV2.S has demonstrated a similar safety profile to that observed in clinical trials. Serious ARs observed in the post-marketing experience including TTS, GBS, ITP, and VTE occurred very infrequently, are adequately monitored, and do not outweigh the significant benefits of single dose vaccination with Ad26.COV2.S. The current post-authorisation exposure is insufficient to establish differences in the onset and severity of these very rare ADRs between primary and booster usage of Ad26.COV2.S.

Integrated Benefit-Risk Evaluation Conclusions

Despite increasing numbers of vaccinated subjects, the ongoing SARS-CoV-2 pandemic remains a public health issue of international concern. The emergence of new virulent lineages has fuelled the need for highly effective preventive measures. Effective and safe COVID-19 vaccines remain a pivotal tool for controlling the disease.

Ad26.COV2.S demonstrated high efficacy against severe/critical disease caused by SARS-CoV2 and protection against hospitalisation and death in clinical trial settings. Analysis of

spontaneous reports of vaccination failure did not show trends for lack of efficacy. Altogether, the totality of data supports that vaccination with Ad26.COV2.S remains efficacious against severe/critical COVID-19, including hospitalisations and deaths related to COVID-19, including against some emerging variants. Data on booster usage (homologous or heterologous) suggests increased effectiveness in protecting against COVID-19 including some VOC, VOI.

As of 31 August 2022, over 52,684,577 doses of the Ad26.COV2.S vaccine have been administered (CDC 2022, ECDC 2022a, KDCA 2022). Increasing experience based on spontaneous/solicited post-marketing reporting of AEs, have led to the identification of SAEs/reactions such as TTS, GBS, and ITP). These risks occur very infrequently, are adequately monitored and do not outweigh the significant benefits of single dose vaccination with Ad26.COV2.S in controlling the global pandemic. Potential safety concerns will continue to be monitored.

A quantitative Benefit-Risk Assessment (qBRA) was conducted to review the differences between hospitalisation and death amongst the vaccinated or the unvaccinated patients who had experienced TTS or GBS. Patients were 18 years of age or older. The current benefit-risk assessment relies on newly published estimates of the Janssen vaccine primary and booster doses duration of effectiveness during Omicron predominance. Based on SARS-CoV-2 hospitalisation and mortality rates estimated during Omicron predominance, the number of COVID-19 hospitalisation and death cases averted by the Janssen primary dose and booster was higher than the number of induced AEs/fatal AEs regardless of age or sex. For one million females aged 18 years and over, the primary dose would avert 508 COVID-19 deaths and 2,884 COVID-19 hospitalisations while being associated with 1.6 to 4.7 TTS cases during Omicron predominance. For one million adult females during Omicron predominance, the booster dose would avert 1,139 COVID-19 deaths and 6,466 COVID-19 hospitalisations while being associated with 0.5 to 1.3 TTS cases. Based on this assessment the benefit-risk profile of the Janssen COVID-19 vaccine remains positive; the MAH will continue to monitor the benefit-risk profile of Ad26.COV2.S as Omicron predominance wanes and when other variants, perhaps with different transmission intensity and severity characteristics, are circulating. Additional information on this analysis can be found in Appendix 9.8.

Taking into account the safety data cumulatively, the overall benefit-risk assessment remains favourable for Ad26.COV2.S when used as recommended in the currently approved indications for both primary and booster active immunisation to prevent COVID-19 infection caused by SARS-COV-2 virus in adults ≥18 years of age.

19. CONCLUSIONS AND ACTIONS

During this reporting period, facial paralysis (including Bell's palsy) and venous thromboembolism were added to the CCDS as post-marketing adverse drug reactions. These new adverse drug reactions do not change the established positive benefit/risk profile of Ad26.COV2.S. Ad26.COV2.S continues to have a favourable benefit-risk profile when used as recommended in the currently approved indications. The Company will continue to monitor potential safety

concerns in association with the use of Ad26.COV2.S. Continuous Company safety monitoring will ensure that up to date safety information is available.

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