JCOVDEN : Periodic safety update report assessment

25 February 2023 to 24 February 2024

This document consists of:

1. The PRAC assessment report of the JCovden periodic safety update report (PSUR) covering the period 23 February 2023 to 24 February 2024 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/439796/2024
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC PSUR assessment report

PRAC assessment report

Procedure no.: EMEA/H/C/PSUSA/00010916/202402

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

Period covered by the PSUR: 25/02/2023 To: 24/02/2024

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:	6 June 2024	6 June 2024
☐	PRAC Rapporteur's preliminary assessment report (AR)	5 August 2024	18 July 2024
☐	MS/PRAC members and MAH comments	4 September 2024	23 August 2024
☒	PRAC Rapporteur's updated assessment report following comments	19 September 2024	23 September 2024
☐	Oral explanation	<Date>	<Date>
☐	PRAC recommendation	3 October 2024	

Procedure resources	
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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 fifth Periodic Safety Update Report (PSUR) for COVID-19 vaccine Janssen (Ad26.COV2.S); covering data for the period from 25 February 2023 to 24 February 2024.

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

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

During the PSUR interval a total of 48,868,800 doses of Ad26.COV2.S vaccine were distributed worldwide, which is a significant decrease compared to the previous reporting period (01 September 2022 to 28 February 2023; 120,564, 550 dosages). A total of 247,007 doses of Ad26.COV2.S vaccine were administered worldwide during the reporting period. In the EU the largest number of administered doses was in Poland (23,041) and Belgium (3,255).

During the reporting period, the MAH submitted one type II variation in EU reflecting the important potential risk of myocarditis and pericarditis in the RMP. This update also included an addition of a warning in section 4.4 and an inclusion of myocarditis and pericarditis as ADRs with frequency not known in section 4.8 of the SmPC (II/0072/G).

During the reporting interval the following signals were closed: Cerebral haemorrhage (not confirmed), heavy menstrual bleeding (not confirmed), myocarditis and pericarditis (confirmed with subsequent implementation in the SmPC, see above), postural orthostatic tachycardia syndrome (not confirmed), appetite disorders (not confirmed) and encephalitis including acute disseminated encephalomyelitis (not confirmed). There were no signals that were undergoing evaluation at data-lock date of the PSUR.

During the reporting interval, "Myocarditis and pericarditis" was added as an important identified risk to the RMP. Furthermore, "Interaction with other vaccines" was removed from missing information and the important potential risk "Immune thrombocytopenia" was reclassified to an important identified risk with renaming to "Thrombocytopenia, including immune thrombocytopenia."

Assessment of the data within the current PSUSA does not provide significant new safety information to the known safety profile of the vaccine.

On 16th February 2024, EMA's Emergency Task Force (ETF) issued a statement on the use of recently updated COVID-19 vaccines recommending that the most recently updated COVID-19 vaccines should be used to provide optimal protection against circulating strains. As SARS-CoV-2 circulates and evolves, new SARS-CoV-2 variants continue to emerge with the ability to evade immunity induced by prior infection or vaccination. Consequently, COVID-19 vaccines require regular strain updates, a situation very similar to the regularly updated influenza vaccines where all marketing authorisation holders are expected to update the composition of their authorised vaccines in accordance with this recommendation.

ETF concluded that EU Member States are recommending that people in the EU/EEA at increased risk for severe COVID-19 disease should be offered vaccination. To provide optimal protection against circulating strains, ETF recommends that the most recently updated COVID-19 vaccines should be used. The ETF recognizes that, in the future, new COVID-19 vaccines may initially be authorised with a composition that does not match circulating VOCs but reflects the composition of the vaccines used in pre-licensure clinical trials. Whenever this occurs, similarly to influenza, the vaccines are expected to be updated before

deployment to reflect recent and/or circulating SARS-CoV-2 variants. The ETF will continue to evaluate SARS-CoV-2 epidemiological data and provide updated vaccine composition recommendations as appropriate.

After the DLP of this PSUR, the MAH reported 31 March 2024 as the marketing cessation date in EU, based on commercial reasons. The MAH informed that the last doses for use in non-EU countries will expire end of September 2024.

On 30 April 2024, ETF recommended updating COVID-19 vaccines to target the new JN.1 variant for the 2024/2025 vaccination campaign. All marketing authorisation holders are expected to update the composition of their authorised vaccines in accordance with this recommendation. Upon enquiry by the EMA, the MAH of JCovden clarified that they did not intend to update their vaccine to any of the recommended variants of concerns (VOC), including XBB and any following.

Finally, the MAH requested to withdraw the marketing authorisation (EU/1/20/1525/001, EU/1/20/1525/002) for JCovden (EMEA/H/C/005737) on 10 June 2024. The marketing authorisation for JCovden was withdrawn on 9th August 2024 (adopted by the European Commission on 26 July 2024). No valid marketing authorisation is therefore available in the EU/EEA at this time. However, the MAH is asked to shortly and concisely present the safety data gathered from the DLP of this PSUR (24th February 2024) up to the final use of this product (expiry date end of September 2024) in an ad-hoc PSUR to be assessed by the PRAC. This PSUR should be submitted before the end of 2024.

3. Recommendations

Based on the PRAC Rapporteur review of data on safety and efficacy, the PRAC is of the view that the reported data does not warrant an update to the product information.

Based on the European Commission Decision issued on 26th July 2024 this product is currently withdrawn from the European market.

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

The MAH is asked to shortly and concisely present the safety data gathered from the DLP of this PSUR (24th February 2024) up to the final use of this product (expire date end of September 2024) in an ad-hoc PSUR to be assessed by the PRAC. This should be submitted before the end of 2024.

5. PSUR frequency

Based on the European Commission Decision issued on 26th July 2024 this product is currently withdrawn from the European market.

The MAH is asked to shortly and concisely present the safety data gathered from the DLP of this PSUR (24th February 2024) up to the final use of this product (expire date end of September 2024) in an ad-hoc PSUR to be assessed by the PRAC. This should be submitted before the end of 2024.

Annex: 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 2023 to 24 February 2024. This is the fifth 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

The IBD for Ad26.COV2.S is 25February 2021 based on the first authorisation in Bahrain.

TAd26.COV2.S is authorised in 61 countries/territories and import licenses have been granted in 22 countries/territories worldwide (see Table 1 and Table 2). In addition, Ad26.COV2.S obtained an Emergency Use Listing by the World Health Organisation (WHO).

Table 1: List of Countries/Territories Where Ad26.COV2.S is Authorised (n=61)

Austria	France	Lichtenstein	Slovakia
Bahamas	Gambia	Lithuania	Slovenia
Bangladesh	Georgia	Luxembourg	Solomon Island
Belgium	Germany	Malta	South Africa
Belize	Ghana	Mauritius	South Korea
Brazil	Greece	Moldova	Spain
Bulgaria	Guatemala	Nepal	Sweden
Central African Republic	Guyana	Netherlands	Syria
Chile	Haiti	New Zealand	Trinidad and Tobago
Comoros	Hungary	Nicaragua	Uganda
Croatia	Iceland	Norway	United Kingdom (Great Britain)
Cyprus	India	Panama	United Kingdom (Northern Ireland)
Czech Republic	Ireland	Papua New Guinea	Vanuatu
Denmark	Italy	Poland	
Estonia	Laos	Portugal	
Finland	Latvia	Romania	

Key: n=Number of Countries/Territories

Table 2: List of Countries/Territories Where Ad26.COV2.S is Granted Import Licences (n=22)

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

Key: n=Number of Countries/Territories

Rapporteur assessment comment:

The IBD of Ad26.COV2.S is based on the first regulatory approval in Bahrain on 25 February 2021. In the EU Ad26.COV2.S was authorized on 11/03/2021. AD26.COV2.S is authorised in total 61 countries/territories worldwide and thus in 43 countries less compared to the last PSUR period.

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 Interval

Date	Country/Territory	Issue	Action Taken
14 April 2023	European Union	Identification of ESI on 31 March 2023: Analysis of available safety data show an increase in the risk for myocarditis and pericarditis following Ad26.COV2.S vaccination (particularly in males under the age of 40 years in the first 2 weeks following vaccination).	Submission of Type II variation on 14 April 2023 to update EUPI and EU-RMP of JCOVDEN to reflect the important identified risk of myocarditis and pericarditis.

Key: DLP–Data Lock Point; ESI–Emerging Safety Issue; EUPI–European Union Prescribing Information; EU-RMP–European Union Risk Management Plan

Rapporteur assessment comment:

During the reporting period, the MAH submitted one type II variation in EU reflecting the important potential risk of myocarditis and pericarditis in the RMP. This variation also included an addition of a warning in section 4.4 and an inclusion of myocarditis and pericarditis as ADRs with frequency not known in section 4.8 of the SmPC (II/0072/G).

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 interval is dated 22 November 2023. Significant changes to the CCDS (ie, CCSI) made within the reporting interval are listed in Table 4 below.

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

CCDS Version and Date	CCDS Section	Description of Change(s)
Version 016 Dated 22 November 2023	Interactions	Updated text for concomitant use with other vaccines
	Adverse Reactions	Added reactogenicity following administration of TRADENAME with seasonal quadrivalent influenza vaccine (SD or HD) was higher than the vaccines administered alone.
Version 015 Dated 10 October 2023	Adverse Reactions	Addition of post-marketing term "immune thrombocytopenia."
Version 014 Dated 05 April 2023	Warnings and Precautions	Addition of warning related to an increased risk of myocarditis and pericarditis in males younger than 40 years of age.
	Adverse Reactions	Addition of terms myocarditis and pericarditis as post-marketing adverse reactions.
		Addition of term "transverse myelitis" to the post-marketing section

Key: CCDS–Company Core Data Sheet; HD–High Dose; SD–Standard Dose

Rapporteur assessment comment:

It is noted that during the reporting interval the CCSI was updated to include the following information: Concomitant use with quadrivalent influenza vaccine (higher reactogenicity with concomitant administration compared to single administration of covid-19 vaccine) and a warning related to increased risk of myocarditis and pericarditis in male subjects <40 years of age. In addition, the terms immune thrombocytopenia, transverse myelitis, myocarditis and pericarditis have been added to the post-marketing section.

1.3.3. Estimated exposure and use patterns

Cumulative Subject Exposure in Clinical Trials

Overall, an estimated 82,240 healthy subjects have been enrolled in the Ad26.COV2.S clinical programme, of which approximately 68,705 subjects received Ad26.COV2.S in the Company-sponsored interventional clinical trials (see Table 5). Of these, 667 subjects were exposed to Ad26.COV2.S in the Phase 1 trials, 935 subjects to Ad26.COV2.S in a Phase 1/2a trial, 2,419 subjects to Ad26.COV2.S in the Phase 2 trials,4 and 64,684 subjects to Ad26.COV2.S in the Phase 3 trials.
Additionally, 16,142 subjects were exposed to Ad26.COV2.S in the pre-approval access programmes, and 729,517 subjects to Ad26.COV2.S in the interventional clinical studies sponsored by other organisations/institutions.

Table 5: Estimated Cumulative Subject Exposure From Clinical Trials

Treatment	Number of Subjects
Ad26.COV2.S	68,705
Comparator	N/A
Placebo	39,413

Note: Number of participants exposed to at least one study vaccine, recorded in the study databases up to cut-off date (24 February 2024).Trials included: VAC31518COV1001, VAC31518COV1002, VAC31518COV1003, VAC31518COV2001, VAC31518COV2004, VAC31518COV2008, VAC31518COV3001, VAC31518COV3003, VAC31518COV3005, VAC31518COV3006, VAC31518COV3009, and VAC18193RSV2008.
A total of 25,878 participants (506 participants from Trial VAC31518COV1001; 150 participants from Trial VAC31518COV2001; 16,047 participants from Trial VAC31518COV3001; 781 participants from Trial VAC31518COV3005; 151 participants from Trial VAC31518COV3006; and 8,243 participants from Trial VAC31518COV3009) that received a regimen with both Ad26.COV2.S and placebo, participants are counted for both, Ad26.COV2.S and placebo.
Key: N/A=Not Applicable

Table 6: Cumulative Subject Exposure to Ad26.COV2.S from Completed Clinical Trials by Age and Sex

Age Range (Years)	Number of Subjects			
	Male	Female	Undifferentiated[b]	Total[a]
12-17	183	146	0	329
18-40	9,719	7,270	6	16,995
41-64	19,667	17,651	2	37,320
65-75	5,605	5,036	0	10,641
>75	937	752	0	1,689
Total	**36,111**	**30,855**	**8**	**66,974**

a: Data from completed clinical trials as of 24 February 2024.
Completed clinical trials included: VAC31518COV1001, VAC31518COV1002, VAC31518COV1003, VAC31518COV2001, VAC31518COV2008, VAC31518COV3001, VAC31518COV3005, VAC31518COV3006, and VAC31518COV3009.
b: The "undifferentiated" column refers to participants whose sex was reported as "undifferentiated" or "intersex" on the Case Report Form.

Table 7: Cumulative Subject Exposure to Ad26.COV2.S from Completed Clinical Trials by Race[a]

Race Group	Number of Subjects
American Indian or Alaska Native	4,407
Asian	4,008
Black or African American	10,445
Native Hawaiian or other Pacific Islander	150
White	43,485
Multiple	2,625
Unknown	729
Not reported	1,125
Missing	0
Total	**66,974**

a: Data from completed trials as of 24 February 2024.
Completed clinical trials included: VAC31518COV1001, VAC31518COV1002, VAC31518COV1003, VAC31518COV2001, VAC31518COV2008, VAC31518COV3001, VAC31518COV3005, VAC31518COV3006, and VAC31518COV3009.

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 2023) for the United States (US), European Centre for Disease Prevention and Control (ECDC 2023) for European Economic Area (EEA) countries/territories, Korea Disease Control and Prevention Agency (KDCA 2023) for South Korea, Ministério da Saúde (Ministério da Saúde 2021) for Brazil, and National Department of Health (NDH 2023) 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 interval (01 March 2023 to 29 February 2024) is provided in Table 8.

Table 8: Subject Exposure to the Ad26.COV2.S Vaccine During the Reporting interval (01 March 2023 to 29 February 2024)

Region/Country/Territory	Number of Distributed Doses[a]	Number of Administered Doses[b,c]
EEA		
Austria	0	151
Belgium	0	3,255
Bulgaria	0	1,399
Croatia	0	974
Cyprus	0	42
Czechia	0	272
Estonia	0	140
France	0	315
Greece	0	485
Hungary	0	472
Iceland	0	4
Ireland	0	97
Italy	0	5
Latvia	0	79
Lithuania	0	21
Luxembourg	0	22
Norway	0	36
Poland	0	23,041
Portugal	0	2,367
Romania	0	725
Slovakia	0	88
Spain	0	552
ROW		
Afghanistan	3,235,200	NR
Burkina Faso	2,832,000	NR
Burundi	151,200	NR
Cameroon	1,209,600	NR
Central African Republic	1,468,800	NR
Chad	1,101,600	NR
Congo, (Brazzaville)	2,995,200	NR

Côte D'ivoire	2,371,200	NR
Equatorial Guinea	400,800	NR
Ethiopia	1,634,400	NR
Ghana	1,821,600	NR
Guinea	794,400	NR
Guinea-Bissau	40,800	NR
Haiti	463,200	NR
Kenya	2,076,000	NR
Lesotho	81,600	NR
Liberia	60,000	NR
Madagascar	2,419,200	NR
Malawi	1,046,400	NR
Mali	1,999,200	NR
Mauritania	480,000	NR
Niger	2,200,800	NR
Papua New Guinea	302,400	NR
Senegal	811,200	NR
Sierra Leone	403,200	NR
Somalia	2,601,600	NR
South Africa	0	187,249
South Korea	0	561
South Sudan	993,600	NR
Sudan	5,534,400	NR
Syria (Damascus)	91,200	NR
Syria (North-West)	300,000	NR
Tajikistan	451,200	NR
Togo	453,600	NR
Uzbekistan	3,000,000	NR
Yemen	19,200	NR
Zambia	3,024,000	NR
US	***0***	***24,655***
Total	**48,868,800**	**247,007**

Key: CDC=Centers for Disease Control and Prevention; COVID-19=Coronavirus Disease-2019; 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 the CDC for the US, from the ECDC for the EEA countries/territories, from the KDCA for South Korea, and from the NDH for South Africa.

c: As of 09 August 2021, all entities have the ability to update or delete their previously submitted records. The use of this new functionality may result in fluctuations across metrics on the CDC COVID-19 Data Tracker as historical data are updated or deleted. The functionality will also allow for more accurate reporting and improved data quality. All reported numbers may change over time as historical data are reported to the CDC. In addition, the information within the ECDC website stated that, "*All data are subject to retrospective correction*" which may be a reason for decrease in the cumulative exposure in certain countries/territories. Exposure values were obtained from the most current counts as of 29 February 2024.

A total of 48,868,800 doses of Ad26.COV2.S vaccine were distributed worldwide from 01 March 2023 to 29 February 2024.

A total of 247,007 doses of Ad26.COV2.S vaccine were administered worldwide from 01 March 2023 to 29 February 2024.

Cumulative Exposure Estimates

The cumulative subject exposure for the Ad26.COV2.S vaccine from launch to 29 February 2024 is provided in Table 9.

Table 9: Cumulative Subject Exposure to the Ad26.COV2.S Vaccine (Launch to 29 February 2024)

Region/Country/Territory	Number of Distributed Doses[a]	Number of Administered Doses[b,c]
EEA		
Austria	1,292,400	368,544
Belgium	629,200	431,825
Bulgaria	1,777,300	531,830
Croatia	1,135,150	205,687
Cyprus	190,500	31,075
Czechia	547,200	414,024
Denmark	1,198,800	45,384
Estonia	110,800	79,490
Finland	68,400	NR
France	3,416,300	1,090,907
Germany	7,818,150	3,753,219
Greece	1,521,600	786,508
Hungary	4,309,200	346,000
Iceland[d]	33,500	54,327
Ireland	281,500	241,743
Italy	2,370,000	1,483,508
Latvia	767,800	294,293
Liechtenstein	NR	264
Lithuania[d]	287,200	295,958
Luxembourg	80,200	41,511
Malta	226,800	32,421
Netherlands	2,464,800	750,752
Norway	403,900	7,435
Poland	15,523,300	3,007,456
Portugal[d]	993,600	1,141,885
Romania	4,080,300	2,069,528
Slovakia	475,200	186,679
Slovenia	230,400	135,358
Spain	2,659,000	1,982,248
Sweden	55,200	NR
ROW		
Afghanistan	20,832,050	NR
Algeria	6,508,800	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	6,889,250	NR
Burundi	453,600	NR
Cambodia	1,060,100	NR
Cameroon	6,010,250	NR
Canada	168,000	NR
Central African Republic	4,543,500	NR
Chad	11,465,650	NR
Colombia	11,504,800	NR
Congo (Brazzaville)	5,691,800	NR
Congo, (Kinshasa)	22,965,600	NR
Côte D'ivoire	8,145,400	NR
Djibouti	446,400	NR
Egypt	15,513,450	NR
Equatorial Guine	400,800	NR
Ethiopia	43,394,150	NR
Gabon	866,400	NR
Gambia	777,600	NR
Ghana	11,661,600	NR
Grenada	2,400	NR
Guinea	3,388,800	NR
Guinea-Bissau	1,639,200	NR
Guyana	96,000	NR
Haiti	811,200	NR
Jamaica	216,000	NR
Kenya	17,020,250	NR
Lao PDR	1,771,200	NR
Lebanon	336,000	NR
Lesotho	1,553,850	NR
Liberia	3,271,200	NR
Madagascar	7,209,950	NR
Malawi	6,960,350	NR
Mali	5,332,750	NR
Mauritania	2,964,000	NR
Mauritius	439,200	NR
Mexico	1,350,000	NR
Moldova	302,400	NR
Morocco	302,400	NR
Mozambique	8,989,700	NR
Namibia	676,800	NR
Nepal	3,711,500	NR
Nicaragua	993,600	NR
Niger	7,939,200	NR
Nigeria	75,009,250	NR
Papua New Guinea	1,123,200	NR
Philippines	12,725,650	NR
Rwanda	897,600	NR
Saint Lucia	12,000	NR

Saint Vincent and Grenadines	7,200	NR
Sao Tome and Principe	100,800	NR
Senegal	3,001,500	NR
Sierra Leone	4,651,200	NR
Solomon Islands	100,800	NR
Somalia	2,601,600	NR
South Africa	30,999,200	8,132,856
South Korea	3,411,000	1,515,847
South Sudan	6,856,250	NR
Sudan	22,846,700	NR
Swaziland	302,400	NR
Switzerland	200	NR
Syria (Damascus)	91,200	NR
Syria (North-West)	300,000	NR
Syrian Arab Republic (Syria)	3,458,400	NR
Tajikistan	451,200	NR
Tanzania, United Republic of	34,890,150	NR
Togo	3,074,400	NR
Trinidad and Tobago	259,200	NR
Tunisia	1,540,800	NR
Turkey	832,800	NR
Uganda	23,388,000	NR
Ukraine	1,202,400	NR
Uzbekistan	4,003,150	NR
Vanuatu	43,150	NR
Yemen	1,216,800	NR
Zambia	15,391,050	NR
US	***41,225,650***[e]	***19,007,537***
Total	**660,062,450**[f]	**53,288,029**

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 the CDC for the US, from the ECDC for EEA countries/territories, from the KDCA for South Korea, Ministério da Saúde for Brazil, and from the NDH for South Africa. The data for administered doses for Brazil were last updated by the Ministério da Saúde website on 15 November 2021, and for Germany, the data for administered doses were last updated by ECDC on 17 November 2022.

c: The information within the ECDC website stated that, "*All data are subject to retrospective correction*" which may be a reason for decrease in the cumulative exposure for administered doses in certain countries/territories. Exposure values were obtained from the most current counts as of 29 February 2024.

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: No data on vaccine distribution in the US was reported in LYNX Finance after June 2022.

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

A total of 660,062,450 doses of Ad26.COV2.S vaccine were distributed worldwide from launch to 29 February 2024.

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	227,666	1,748,144
South Korea[a]	0	27,032
US[b]	0	1,565,864
Total	**227,666**	**3,341,040**

Key: KDCA=Korea Disease Control and Prevention Agency; US=United States

a: The data for administered booster doses for South Korea was last updated by KDCA website on 11 December 2022.

b: The counts also include second booster doses administered in the US.

A total of 227,666 subjects were administered the homologous Ad26.COV2.S vaccine booster dose in South Africa from 01 March 2023 to 29 February 2024.

A total of 3,341,040 subjects were administered the homologous Ad26.COV2.S vaccine booster dose in South Africa, South Korea, and the US from launch to 29 February 2024.

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.

Rapporteur assessment comment:

A total of 48,868,800 doses of Ad26.COV2.S vaccine were distributed worldwide from 01 March 2023 to 29 February 2024. In the current reporting period, there has been a significant decrease in distributed doses worldwide compared to the previous reporting period (01 September 2022 to 28 February 2023; 120,564, 550 dosages). A total of 247,007 doses of Ad26.COV2.S vaccine were administered worldwide from 01 March 2023 to 29 February 2024. In the current reporting period, there has been a clear decrease in administered doses worldwide compared to the previous reporting period (01 September 2022 to 28 February 2023; 336,693 doses administered). In the EU the largest number of administered doses was in Poland (23,041) and Belgium (3,255). The distribution and administration of Ad26.COV2.S vaccine in EEA countries decreased further during the current interval.

A total of 660,062,450 doses of Ad26.COV2.S vaccine were distributed worldwide from launch to 29 February 2024. A total of 53,288,029 doses of Ad26.COV2.S vaccine were administered worldwide from launch to 29 February 2024.

1.3.4. Data in summary tabulations

During the reporting interval, 4,970 serious ARs and 6,620 nonserious ARs were received from spontaneous sources, and 112 serious ARs were received from noninterventional post-marketing studies and other solicited sources.11 For the reporting interval of 25 February 2023 to 24 February 2024, the AR count is notably less than the number of the ARs identified from the previous PBRER reporting interval of 25August 2022 to 24 February 2023 (7,626 serious ARs and 14,821 nonserious ARs). This decrease in number may be due to the lower exposure to the vaccine compared to last reporting interval.

From spontaneous sources, noninterventional post-marketing studies, and other solicited sources, the SOCs including the most reported ARs were:

- General Disorders and Administration Site Conditions (3,157)
- Nervous System Disorders (2,066)
- Musculoskeletal and Connective Tissue Disorders (1,171)
- Gastrointestinal Disorders (639)
- Investigations (598)

Cumulatively, 102,388 serious ARs (101,114 spontaneous, 1,274 from noninterventional post-marketing studies and other solicited sources) were received by the MAH.

Rapporteur assessment comment:

It can be agreed that the lower frequency of ARs is due to the significantly lower exposure of the vaccine during this reporting interval compared to previous ones.

No new safety concern was noted here.

1.3.5. Findings from clinical trials and other sources

1.3.5.1. Completed Clinical Trials

A "completed clinical trial" is defined as a trial for which a final CSR is available at the time of the DLD for this PBRER reporting interval.

During the reporting interval, 6 Company-sponsored interventional clinical trials (VAC31518COV1001, VAC31518COV2008, VAC31518COV3001, VAC31518COV3005, VAC31518COV3006, and VAC31518COV3009) of Ad26.COV2.S were completed. The safety summary from these completed clinical **trials is presented below:**

Trial VAC31518COV1001

This was a Phase 1/2a, randomised, double-blind, placebo-controlled, first-in-human, multicentre trial in healthy adults aged ≥18 to ≤55 years and in adults 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 at 6, 12, or 24 months after the primary vaccination regimen administered in Cohort 2. Of the 1,718 participants screened in this trial, a total of 1,076 participants received at least 1 dose of the trial vaccine (Ad26.COV2.S or placebo). A summary of safety data is presented below:

Death, Serious adverse events, Adverse Events leading to discontinuation, and AESIs
A total of 5 deaths were reported. One participant died in the 5×1010 vp, B: PL group (Cohort 2a) due to asphyxia (Grade 4) during the follow-up post-dose 1, which was considered not related to the trial vaccine by the investigator (homicide). One participant died in the 5×1010 vp, 5×10^{10} vp, B: PL group (Cohort 2b) due to suicide (Grade 4) during the follow-up post-booster 1, which was considered not related to the trial vaccine by the investigator. In total, 3 fatal SAEs were reported after unblinding in participants who had already completed their planned vaccination regimen at the time of unblinding (cardiac arrest, haemorrhage intracranial, and aortic aneurysm), all of which were reported in Cohort 3 (including participants ≥65 years). None of these 3 fatal events were considered related to the trial vaccine by the investigator. Before unblinding, SAEs were reported in 16 participants and after unblinding, SAEs were reported in 36 participants. Except for 2 SAEs, none of the reported SAEs were considered related to the trial vaccine by the investigator.
The SAEs of pyrexia (Grade 3) and multiple sclerosis (verbatim: worsening of multiple sclerosis; Grade 2) were considered related to the trial vaccine by the investigator. The SAE of pyrexia (reported on 28 July 2020) met the criteria for a trial pause. However, the trial was resumed after Data Review Committee review that same day, and no formal pause to the vaccinations occurred in the trial. The SAE of multiple sclerosis was considered not related by the sponsor (no additional information was available). The SAE was ongoing (resolving) at the time of this report. Twenty-one participants discontinued the trial vaccine due to the following AEs: asphyxia (fatal, homicide), hanging (fatal, suicide), 13 cases of COVID-19, pyrexia, hypertension, nephrolithiasis (SAE), asthma, hypertension, and increased blood pressure. All these AEs were considered not related to the trial vaccine by the investigator, except for pyrexia, hypertension, and increased blood pressure. No AESIs (ie, thrombotic events with concurrent thrombocytopenia) were reported in this trial.
Eight participants had suspected AESIs (thrombotic events and/or thrombocytopenia [defined as platelet count below 150,000/µL,]) in this trial. The suspected AESIs included events of deep vein thrombosis, thrombocytopenia, and ischaemic attack. All suspected AESIs were considered resolved by the time of this report, and all were considered not related to the trial vaccine by the investigator. None of these suspected AESI qualified for review by TTS adjudication committee.

Trial VAC31518COV2008

This was 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 (5×10^{10} vp or 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 (VAC31518COV2008 Cohort 1 - homologous booster) or who previously received primary vaccination with the Pfizer BNT162b2 vaccine (VAC31518COV2008 Cohort 2 - heterologous booster). The significant safety summary from this trial is described below:

Deaths, Serious Adverse Events, Discontinuations due to Adverse Events, and AESIs

There were 2 deaths reported in Cohort 1, 1 malignant neoplasm, and 1 cardiac arrest, 301 days and 98 days post-booster, respectively. Both the AEs led to trial discontinuation. Neither of the fatal events were considered related to booster vaccination. Twenty participants in Cohort 1 and 15 participants in Cohort 2 experienced SAEs not considered related to vaccination.

There were no SAEs considered related to booster vaccination in Cohort 1. In Cohort 2, 1 participant vaccinated at the 2.5×10^{10} vp dose level experienced 5 Grade 3 SAEs which were all considered related to vaccination. The SAEs were asthenia, headache, nausea, fatigue, and myalgia. All the SAEs had resolved by Day 10 post-booster vaccination. The AESIs qualified for assessment if thromboembolic events were reported within 42 days of a report of thrombocytopenia/low platelet counts in the same participant. There were no AESIs that qualified for TTS assessment during the trial. Seven AEs of thrombocytopenias were reported in 6 participants, with onset within 19 days after homologous booster vaccination. Of these 7 AEs of thrombocytopenia, 5 were Grade 1 severity and 2 were Grade 3.

Both Grade 3 thrombocytopenia AEs were considered related to trial vaccination. All AEs of thrombocytopenia resolved within 15 days of detection, except for 1 case which was reported as resolved 34 days after onset.

Trial VAC31518COV3001

This was 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 was evaluated in participants living in, or going to, locations with high risk for acquisition of SARS-CoV-2 infection after administration of trial vaccine. All participants who initially received placebo in the double-blind phase were offered a single dose ofAd26.COV2.S at the Month 6/Unblinding Visit. Additionally, the open-label phase of the trial was extended to include an open-label booster vaccination with a single dose of Ad26.COV2.S at the Year 1/Booster Visit. With Protocol Amendment 7, active follow-up of suspected COVID-19 episodes was replaced by passive follow-up (open-label passive follow-up phase). Passive follow-up consisted of safety follow-up phone call visits by the site instead of on-site visits to document safety of the vaccine (such as SAEs or AESIs) and COVID-19 events as (S)AEs and Medically-Attended Adverse Events (MAAEs). A total of 49,498 participants were screened, of whom 43,788 were randomised and vaccinated with the trial vaccine at Day 1 in a 1:1 ratio (21,898 vaccinated with Ad26.COV2.S and 21,890 received placebo). A summary of safety data is presented below:

The open-label active follow-up phase (active follow-up of suspected COVID-19 cases) consisting of:

- The active open-label Ad26.COV2.S cross-over vaccination phase of the placebo group (starting from the unblinding date until the booster visit), and
- The active open-label Ad26.COV2.S booster vaccination phase (starting from the booster visit until site approval of Protocol Amendment 7).
  The open-label passive follow-up phase (passive follow-up of suspected COVID-19 cases instead of the active follow-up of suspected COVID-19 in the former phases of the trial, as of site approval of Protocol Amendment 7).

Deaths, Serious Adverse Events, Discontinuations due to Adverse Events, and AESIs

For the entire double-blind and open-label active phase, the incidence of fatal AEs was0.42 per 100 PY FU in the Ad26.COV2.S group (186 cases) and 0.77 per 100 PY FU in the placebo group (65cases), all of which were considered not related to the study vaccine(Ad26.COV2.S or placebo) by the investigator. All deaths reported after Ad26.COV2.S booster vaccination belonged to the late booster group with an incidence of 0.40 per 100 PY FU (55 cases). No deaths were reported in the early booster group (likely due to the small sample size).

For the entire open-label passive phase, the incidence of fatal AEs was 0.51 per 100 PY FU (35cases) in the Ad26.COV2.S group. No deaths were reported in the placebo group, due to the very low sample size compared to the Ad26.COV2.S group. Most deaths that were reported after Ad26.COV2.S booster vaccination belonged to the late booster group.

During the entire double-blind and open-label active phase, one or more SAEs were reported in the Ad26.COV2.S group with an incidence of 3.55per 100 PY FU compared with the placebo group (4.92 per 100 PY FU). Most of the SAEs belonged to the SOC of infections and infestations (PTs: COVID-19 and COVID-19 pneumonia).

During the entire open-label passive phase, 1 or more SAEs were reported in the Ad26.COV2.S group with an incidence of 2.61 per 100 PY FU compared with the placebo group (9.23 per 100 PY FU). Most SAEs were not associated with COVID-19 and reported in the Ad26.COV2.S group with an incidence of 2.58 per 100 PY FU compared with the placebo group (9.23 per 100 PY FU).

One SAE of a thromboembolic event with thrombocytopenia (PTs: Venous transverse sinus thrombosis and Cerebral haemorrhage) was classified as TTS meeting both Level 1 criteria using the BC level of certainty and the Centers for Disease Control and Prevention definition for a Tier 1 TTS case. The case met the PRAC criteria of a Confirmed case of TTS.

Fewer AEs were reported in the homologous Ad26.COV2.S booster group compared to the heterologous booster groups (Ad26.COV2.S booster after 2 doses of mRNA group and Ad26.COV2.S booster after any other schedule group). Overall, a higher reactogenicity profile was observed for the heterologous booster groups compared with the homologous Ad26.COV2.S booster group. During the open-label passive phase, the number of AEs/SAEs reported was reduced compared to the combined double-blind and open-label active phase, as this might be expected due to the nature of the follow-up. No difference was observed in the safety profile of the Ad26.COV2.S booster when received within 6 months (early booster) or more than 6 months (late booster) after the first Ad26.COV2.S dose. Beyond the single TTS case reported during the double-blind phase of the study, no new cases of TTS were identified. There were less AEs observed post-dose 2 of Ad26.COV2.S compared to post-dose 1 ofAd26.COV2.S. In the combined double-blind and open-label active phase, there were more fatal AEs reported compared with the open-label passive phase. Most fatal AEs were reported in the Ad26.COV2.S group of which all were considered not related to the study vaccine. Related SAEs either associated or not associated with COVID-19 were reported less in the open-label passive phase compared to the combined double-blind and open-label active phase. No conclusions can be drawn for the mixed schedule group.
During the entire trial, 4 AEs leading to termination of study participation were reported in 3 participants after receiving at least 1 dose of Ad26.COV2.S. All events were reported in the late booster group (Grade 3 myocardial infarction and Grade 3 pneumonia in 1 participant, Grade 3 glioblastoma in 1 participant, and Grade 1 alopecia in the other participant). In the placebo group, 5 events were reported in 2 participants (1 participant reported an AE of Grade 3 ophthalmic herpes zoster and another participant reported AEs of Grade 3 acute kidney injury, Grade 4 COVID-19, and 2 events of Grade 4 fall). None of the events were considered related to the study vaccine by the investigator. No AEs leading to study discontinuation were reported in participants that received Ad26.COV2.S as a heterologous booster.

Trial VAC31518COV3005

This was a Phase 3, randomised, double-blind, parallel, multicentre trial to evaluate the safety, reactogenicity, and immunogenicity of Ad26.COV2.S co-administered with a quadrivalent standard-dose in participants 18 years and above (≥18 to ≤64 years) or high dose seasonal influenza vaccine in participants 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. A summary of the safety findings from this trial is presented below:

Deaths, Serious Adverse Events, Discontinuations due to Adverse Events, AESIs

An AE with fatal outcome (Grade 4 cardiac arrest) was reported in 1 (2.1%) participant in Group 3 after concomitant administration of the Ad26.COV2.S and influenza vaccine (high dose). This participant had the following active medical conditions at study entry: atrial fibrillation, hypertension, type 2 diabetes mellitus, and gastroesophageal reflux disease. The event was considered by the investigator as not related to the study vaccines.

Serious adverse events were reported in 2.4% (9/382) of participants in Group 1, 1.8% (7/384) of participants in Group 2, 2.1% (1/47) of participants in Group 3, and 4.3% (2/46) of participants in Group 4. Most SAEs were Grade 3 in severity. Two SAEs were Grade 4 in severity (cardiac arrest and pulmonary embolism). None of the SAEs were considered related to study vaccine by the investigator, except for the event of deep vein thrombosis in 1 participant in Group 1 and the events of thrombocytopenia in 1 participant in Group 1 and 1 participant in Group 2.

Adverse events leading to permanent discontinuation of vaccination were reported in 1 (0.3%) participant in Group 1 after concomitant administration of Ad26.COV2.S and influenza vaccine (standard dose) (Grade 2 urticaria considered related to study vaccine) and
in 1 (2.1%) participant in Group 3 after concomitant administration of Ad26.COV2.S and influenza vaccine (high dose) (Grade 4 cardiac arrest).

In the standard-dose groups, the following suspected AESIs were reported: deep vein thrombosis (in 1 participant in Group 1), heparin-induced thrombocytopenia12 (in 1 participant in Group 1), pulmonary embolism (in 1 participant in Group 2), thrombocytopenia (in 5participants in Group 1 and 9 participants in Group 2) and platelet count decreased (in 2 participants in Group 1 and 3 participants in Group 2). None of the participants had thrombosis and thrombocytopenia concomitantly; therefore, none of the suspected AESIs qualified for TTS assessment.

Concomitant administration of the vaccines did not impact the durability of the influenza- and SARS-CoV-2-specific humoral immune responses as there were no relevant differences between the Co-Administration CoAd and control groups during the 6-month follow-up period. This was also reflected in similar seroprotection and seroconversion rates between the groups and across the 4 influenza vaccine strains.

Trial VAC31518COV3006

This was a Phase 2, randomised, observer-blind trial to evaluate the safety, reactogenicity, and immunogenicity of different dose levels of Ad26.COV2.S administered as a 1- or 2-dose regimen in healthy adolescents aged 12 to 17 years inclusive. A summary of safety findings from this trial is presented below:

Deaths, Serious Adverse Events, Discontinuations due to Adverse Events, AESIs

One death by intentional overdose (intentional calcium channel blocker overdose) was reported in the 1.25×10^{10} vp dose group in the 1 dose primary regimen during the booster follow-up 1 period. This fatal AE was considered not to be related to the study vaccine by the investigator.

Following SAEs were reported in 3 participants: Grade 3 femur fracture, Grade 3 vaginal cyst excision, and 1 fatal SAE of Grade 4 intentional overdose (intentional calcium channel blocker overdose). These SAEs were not considered related to study vaccine by the investigator.

No AEs leading to study vaccine discontinuation were reported in any dose group. Thrombosis with TTS and Multisystem Inflammatory Syndrome (in Children) (MIS-C) were considered AESIs in this trial. One participant experienced an event of platelet count decreased 1 day after the first vaccination, that was evaluated as a case of suspected AESI. The suspected AESI did not qualify for TTS assessment as the participant did not have thrombosis and thrombocytopenia concomitantly, thus, no case of TTS was detected in this trial. Also, no cases of MIS-C were reported during the trial.

Trial VAC31518COV3009

This was 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 was 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.

All eligible participants who initially received placebo in the double-blind phase were offered a single dose of Ad26.COV2.S (open-label vaccination) and subsequently, eligible participants who only received a single Ad26.COV2.S vaccination were offered an open-label booster vaccination. All booster vaccinations have now been completed. The following phases are included as presented in the Study Overview below:

- The double-blind phase (starting from the date of first study vaccination until the unblinding date)

- The open-label active follow-up phase (active follow-up of suspected COVID-19 cases starting from the unblinding date until site approval of Protocol Amendment 7)

- The combined double-blind and open-label active phase (starting from the date of first study vaccination until site approval of Protocol Amendment 7)

- The open-label passive follow-up phase (passive follow-up of suspected COVID-19 cases instead of the active follow-up of suspected COVID-19 in the former phases of the trial, as of site approval of Protocol Amendment 7

At the end-of-study analysis, a total of 31,705participants were included in the Full Analysis Set (FAS) ofthe combined double-blind and open-label active phase. For the open-label passive phase, 24,342 participants were included in the FAS7 (at study start, 13,094 participants received Ad26.COV2.S and 11,248 participants received placebo). For the analysis of safety, data are compared between 24,105participants who had received at least one dose of Ad26.COV2.S and 15,613 placebo recipients from the combined double-blind and open-label active phase. Additionally, safety data for the open-label passive phase are compared between 11,043 participants who had received at least 1 dose of Ad26.COV2.S during the combined double-blind and open-label active phase and the 360 participants who remained in the placebo group at the time of study site approval of Protocol Amendment 7. A summary of safety data is presented below:

Deaths, Serious Adverse Events, Discontinuations due to Adverse Events, AESIs

For the entire double-blind and open-label active phase, the incidence rates of 1 or more fatal AEs (including COVID-19 related deaths) were comparable with 0.30 per 100 PY FU in at least 1 dose Ad26.COV2.S group (in 71 participants) and 0.38 per 100 PY FU (in 17 participants) in the placebo group. All events were considered not related to the study vaccine (Ad26.COV2.S or placebo) by the investigator, except for 1 event of respiratory distress (Grade 4) in 1 participant that was considered related. This participant who received placebo during the double-blind phase was reported with a Grade 4 SAE of respiratory distress on the night of receiving the open-label Ad26.COV2.S. This death was considered related to the placebo vaccination during the double-blind phase by the investigator and was considered not related by the Sponsor. For the entire open-label passive follow-up phase, the incidence of fatal AEs (including COVID-19 related deaths) was 0.30 per 100 PY FU in the at least 1 dose Ad26.COV2.S group (in 21 out of11,043 participants), which were all considered not related to the study vaccine by the investigator. No fatal events were reported for the placebo group (ie, 360 participants).

During the entire double-blind and open-label active phase, 1 or more SAEs were reported in at least 1 dose Ad26.COV2.S group with an incidence of 3.04 per 100 PY FU compared with the placebo group that had a higher incidence of 4.10 per 100 PY FU. Most of the SAEs belonged to the SOC of infections and infestations (PTs: COVID-19 and COVID-19 pneumonia). During the entire open-label passive follow-up phase, 1 or more SAEs were reported in at least 1 dose Ad26.COV2.S group with an incidence of 1.97 per 100 PY FU compared with the placebo group that had a lower incidence of 1.46 per 100 PY FU. Most of the SAEs of at least 1 dose Ad26.COV2.S group belonged to the SOC of infections and infestations with an incidence of 0.33 per 100 PY FU (PTs: Pneumonia and Sepsis). No cases of TTS were identified by the AESI Adjudication Committee during the entire trial. Incidence rates of MAAEs per 100 PY FU were lower in at least 1 dose Ad26.COV2.S group (18.49 per 100 PY FU) compared to the placebo group (31.49 per 100 PY FU) during the combined double-blind and open-label active phase.

1.3.5.2. Ongoing Clinical Trials

An "ongoing clinical trial" is defined as a trial for which the first ICF has been signed, but for which a final CSR is not available at the DLD for this PBRER reporting interval, regardless of whether the last participant last visit has occurred.
During the reporting interval, 3 Company-sponsored, interventional clinical trials (VAC31518COV2004, VAC31518COV3003, and VAC18193RSV2008) of Ad26.COV2.S were ongoing. These clinical trials are briefly summarised below:

Trial VAC31518COV2004: This is a Phase 2, open-label, multicentre trial to evaluate the safety, reactogenicity, and immunogenicity of Ad26.COV2.S in healthy pregnant (2nd and/or 3rd trimester of pregnancy) participants aged ≥18 to ≤45 years. In this trial, Ad26.COV2.S will be assessed as a single dose in pregnant women who were previously vaccinated with another COVID-19 vaccine regimen or who were vaccine naïve at study entry No significant safety findings were identified from this trial during the reporting interval.

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 55years, 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 enrolled 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 TTS events. No significant safety findings were identified from this trial during the reporting interval.

Trial VAC18193RSV2008: This is a Phase 1, randomised, observer-blind, multicentre trial to evaluate innate and pro-inflammatory responses of an Ad26.RSV.preF-based vaccine, Ad26.COV2.S and Ad26.ZEBOV vaccine in adult participants aged 18 to 59 years in stable health. No significant safety findings were identified from this trial during the reporting interval.

Long-term Follow-up
No long-term follow-up information became available during the reporting interval.

Other Therapeutic Use of Medicinal Product
No other programs that follow a specific protocol (solicited reporting as per ICH E2D) were conducted for Ad26.COV2.S during the reporting interval.

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

Findings From Non-Interventional Studies

Based on review of the data from noninterventional study for Ad26.COV2.S during the reporting interval, no new information with potential impact to the benefit-risk assessment has been identified.

Real World Evidence Summary for Ad26.COV2.S

The Company-sponsored (VAC31518COV3021, VAC31518COV4002, VAC31518COV4004, and VAC31518COV4019), collaborative, and publicly available RWE studies/trials reporting on the VE ofAd26.COV2.S are described below. As these studies assessed vaccine effectiveness and not safety, no safety data is reported here:

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 is being 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 DLD of this PBRER, 250,878 participants received Ad26.COV2.S in this study.
In addition, this trial evaluated early VE against hospital admissions of a homologous Ad26.COV2.S boost 4 to 6 months after primary vaccination during the Omicron wave (15November 2021 to 14 January 2022) in HCWs in South Africa (Gray 2022). Vaccine efficacy (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.

Study VAC31518COV4002

Final results (up to 12 months after vaccination; median follow-up ranging from 243 days to 268 days) are available from this study, 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 VE results in Janssen's large, longitudinal US cohort study demonstrated effective and stable VE for the single-dose Ad26.COV2.S, based on month-on-month analysis and Kaplan-Meier plots through the end of September 2022. There have been several other RWE studies that have been recently published by researchers, that evaluate the VE of single-dose Ad26.COV2.S. 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 literature, it is confirmed that there was a benefit to 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 in Study VAC31518COV4002 and the booster dose Ad26.COV2.S in Study VAC31518COV3021.

Study VAC31518COV4004

Final results were available for this study, multicentre, multi-country, hospital-based case-control study with test negative case-control design to assess the absolute effectiveness of a single-dose ofAd26.COV2.S in comparison to no vaccine against laboratory-confirmed SARS-CoV-2 SARI hospitalisations as well as estimate effectiveness for different age groups, those identified with certain chronic conditions, immunocompromised individuals, duration since vaccination, and related to specific SARS-CoV-2 variants. The final results from this study with data collection through February 2023 demonstrated that a single-dose of Ad26.COV2.S provided protection against laboratory confirmed SARS-CoV-2 SARI hospitalisations. This protection persisted for up to 6 months after vaccination. No significant differences were seen when stratified by age, chronic medical condition, time since dose, or period of specific SARS-COV-2 variants. There was lack of precision, particularly for stratified analyses, due to the small number of enrolled vaccine recipients.

Study VAC31518COV4019

Final results (with 12 months of follow-up time from the date of booster vaccination for an exposed individual and the corresponding date for the matched individual in the referent group) were available from this study, an observational, longitudinal cohort study of individuals in the US to assess the relative effectiveness of heterologous and homologous booster vaccination in preventing COVID-19 related hospitalisations in individuals who completed an FDA-authorised or approved COVID-19 primary vaccination series (Ad26.COV2.S [1 dose], BNT162b2 [2 doses], and mRNA-1273 [2 doses]) using both open and closed-claims data elements aggregated by Health Verity.

The final results from this study demonstrated that both homologous and heterologous booster vaccines provided protection against COVID-19 related hospitalisations for up to 12 months. There have been other RWE studies that have been recently published by researchers, that evaluate the VE of single dose and booster Ad26.COV2.S. The protection against COVID-19 varies between different Variants Of Concerns (VOCs). Single dose Ad26.COV2.S VE against infection was reported to be lower during Omicron-emerging and Omicron-predominated periods. Vaccination remained more effective in preventing hospitalisation and death during the Omicron-emerging and Omicron-predominated periods. Vaccine effectiveness against COVID-19 infections and COVID-19-related hospitalisation was observed in fully vaccinated individuals who received a booster dose. Fully vaccinated individuals who received heterologous Ad26.COV2.S or mRNA booster vaccines showed an increase in VE compared with homologous dose Ad26.COV2.S or mRNA vaccines during the Omicron periods as reported in RWE studies. This literature confirms the benefit of a heterologous Ad26.COV2.S booster dose in protecting against COVID-19 related infections, hospitalisations, and deaths, also during the Omicron period.

Rapporteur assessment comment:

During the reporting interval, 6 Company-sponsored interventional clinical trials (VAC31518COV1001, VAC31518COV2008, VAC31518COV3001, VAC31518COV3005, VAC31518COV3006, and VAC31518COV3009) of Ad26.COV2.S were completed. In addition, 3 Company-sponsored, interventional clinical trials (VAC31518COV2004, VAC31518COV3003, and VAC18193RSV2008) of Ad26.COV2.S were ongoing.

No new safety related concerns have been generated in these trials.

1.3.5.3. Other Clinical Trials and Sources

Completed Clinical Study

During the PBRER reporting interval, 1 interventional clinical study (VAC31518COV3012) sponsored by SAMRC was completed for Ad26.COV2.S.

Study VAC31518COV3012 (Sisonke [Together])

This was a Phase 3b, open-label, single-arm, multicentre, implementation Study to evaluate the effectiveness of the single-dose of Ad26.COV2.S among 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.

Safety Summary

Among 477,234 participants who received the single Ad26.COV2.S.dose, 10,279 AEs were reported, of which 138 (1.3%) were SAEs or AESI. Women reported more AEs than men (2.3% versus 1.6%). AE reports decreased with increasing age (3.2% for age 18 to 30 years, 2.1% for age 31 to 45years, 1.8% for age 46 to 55years, and 1.5% for age >55years). Participants with previous COVID-19 infection reported slightly more AEs (2.6% versus 2.1%). The most common reactogenicity events were headache (n=4,923) and body aches (n=4,483), followed by injection site pain (n=2,767) and fever (n=2,731), and most occurred within 48 hours of vaccination. Two cases of thrombosis with thrombocytopenia syndrome and 4 cases of Guillain-Barré syndrome were reported post-vaccination. Most SAEs and AESI (n=138) occurred at lower than the expected population rates. Vascular (n=37; 39.1/100,000 PY) and nervous system disorders (n=31; 31.7/100,000 PY), immune system disorders (n=24; 24.3/100,000 PY), and infections and infestations (n=19; 20.1/100,000 PY) were the most common reported SAE categories. Overall, the single dose of Ad26.COV2.S was well tolerated, effective at preventing severe COVID-19 infection and immunogenic among healthcare workers in South Africa, including PLWH.

Ongoing Clinical Studies

During the PBRER reporting interval, 7 interventional clinical studies sponsored by other organisations/institutions were ongoing for Ad26.COV2.S: 1 interventional clinical study (COV-BOOST [VAC31518COV2009]) sponsored by University Hospital Southampton NHS Foundation Trust; 1 interventional clinical study (VAC31518COV2012) sponsored by Vaccine Trial Centre (Hospital for Tropical Diseases, Mahidol University, Thailand); 1 interventional clinical study (VAC31518COV2016 [AUR1-8-341]) sponsored by The Aurum Institute NPC; 1 interventional clinical study (VAC31518COV3018) sponsored by Mayo Clinic; 1 interventional clinical study (VAC31518COV3021 [Sisonke Boost Open-Label Study {SISONKE2}]) sponsored by SAMRC; 1 interventional clinical study (VAC31518COV4012) sponsored by 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 National Institute of Health. The summary of safety findings from these ongoing clinical studies are presented below:

Study COV-BOOST (VAC31518COV2009)

This is a Phase 2, randomised, multicentre study conducting in the 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 enrolled in 2 or 3 stages. At the time of DLD of this PBRER, 2,878 participants were enrolled, of which 206 received Ad26.COV2.S. During the reporting interval, no relevant safety information related to Ad26.COV2.S from this clinical study became available.

Study VAC31518COV2012

This is a 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 570 participants were recruited. Enrolment of groups are open-label allocation and assessor masked. At the time of DLD of this PBRER, 514 participants were assessed for eligibility and 465 participants received the Ad26.COV2.S in this study. During the reporting interval, no new significant 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 study of the safety and immunogenicity ofCOVID-19 vaccine strategies in 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 enrolled 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 DLD of this PBRER, 231 participants received Ad26.COV2.S in this study. During the reporting interval, no new significant safety findings related to Ad26.COV2.S from this clinical study became available.

Study VAC31518COV3018
This is a Phase 3, prospective, open-label clinical study 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 DLD of this PBRER, 55participants received Ad26.COV2.S in this study. During the PBRER reporting interval, no new significant 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 is being 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 DLD of this PBRER, 250,878 participants received Ad26.COV2.S in this study. During the reporting interval, no new significant safety findings related to Ad26.COV2.S from this clinical study became available.

Study VAC31518COV4012
This is a study in participants >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 Ad26.COV2.S and boosting with either Ad26.COV2.S or 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 and boosting with either Ad26.COV2.S or mRNA vaccines. At the time of DLD of this PBRER, 298 participants received Ad26.COV2.S in this study. During the reporting interval, no new significant 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 DLD of this PBRER, 150 participants received Ad26.COV2.S in this study. During the reporting interval, no significant 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 interval that had an impact on the benefit-risk balance of Ad26.COV2.S.

Rapporteur assessment comment:

During the PBRER reporting interval, 7 interventional clinical studies sponsored by other organisations/institutions were ongoing for Ad26.COV2.S: COV-BOOST [VAC31518COV2009]; VAC31518COV2012; VAC31518COV2016 [AUR1-8-341]); VAC31518COV3018; VAC31518COV3021 and VAC31518COV4012. During the reporting interval, no new safety concerns were identified in these studies.

Medication Errors

Results/Discussion

During this reporting interval, a total of 14 (13 medically confirmed and 1 medically unconfirmed) initial, primary dose cases reporting medication errors were retrieved. There were 3 serious and 11 nonserious cases which reported a total of 17 medication error events of interest (EOI) (2 serious; 15nonserious). During this reporting interval, a total of 17 (9 medically confirmed and 8 medically unconfirmed) post-marketing, initial cases reported as booster dose were identified. Of these 17 cases, there were 14 serious and 3 nonserious cases, which reported a total of 17 medication error EOI (11 serious; 6 nonserious). Of these cases, 14 were heterologous and 3 were homologous.

Post-marketing Sources (Including Spontaneous and Solicited) Cases

Primary Dose

During this reporting interval, a total of 14 (13 medically confirmed and 1 medically unconfirmed) post-marketing, initial, primary dose cases reporting medication errors were retrieved. Of these 14 cases, 5 concerned paediatric patients. The remaining 9 cases reported 12 medication error EOI (2 serious; 10 nonserious) and are presented below. Cumulatively, 2,520 (1,798 medically confirmed and 722 medically unconfirmed) post-marketing, primary dose cases reporting medication errors were retrieved. Of these 2,520 cases, 377 concerned paediatric patients which are discussed in Paediatric Cases below. The remaining 2,143 cases reported a total of 2,883 EOI (37 serious; 2,846 nonserious) of medication error are presented below.

Table 11: Characteristics of Selected Cases Involving the Use of Ad26.COV2.S and Reporting Medication Errors

Case Characteristics		Number of Cases Received During the Reporting interval=9	Number of Cases Received Cumulatively=2,143[a]
Sex	Male	2	714
	Female	3	690
	NR	4	739
Age (Years)[b]	18 to 35	2	322
Minimum: 24	36 to 50	1	303
Maximum:63	51 to 64	2	354
Mean: 44	Adult	1	41
Median: 48	NR	3	930
Sources	Spontaneous	8	2,129
	Clinical study (noninterventional, solicited)	1	14
Country/Territory	United States	5	1,838
	United Kingdom	2	4
	Netherlands	1	11
	South Africa	1	6
Event Characteristics		Number of Events=12	Number of Events=2,883
Seriousness (Event Level)[c]	Nonserious	10	2,846
	Serious	2	37
Outcome (Event Level)[c]	Resolved	1	50
	NR	11	2,791

Key: EOI=Event(s) of Interest; NR=Not Reported

a: For the cumulative column, the counts were presented in decreasing order based on the current reporting interval (25 February 2023 to 24 February 2024).

b: The median and mean age calculation were based on the current reporting interval (25 February 2023 to 24 February 2024). Age group was presented for cases where age was not reported.

c: Seriousness and outcome have been presented for the EOI. A single case may report more than 1 EOI.

Of these 9 post-marketing, primary dose cases received during the reporting interval, the most frequently reported country/territory of origin was US (n=5). These cases concerned 2 males, 3 females, and 4 did not report sex. The age range was from 24 to 63 years. The frequency distribution of the MedDRA PTs of interest reported in cases (n=9) is presented in Table 12. A single case may contain more than 1 EOI. Majority of the cases included the PT of Poor quality product administered, and 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 Cases Reporting Medication Errors With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Reporting Interval[a]		Number of Events Reported Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
Poor quality product administered	0	3	0	712
Product storage error	0	2	2	596
Expired product administered	0	1	4	541
Incorrect dose administered	0	1	2	103
Medication error	1	0	2	119
Overdose	1	0	4	60
Product administration error	0	1	2	66
Product dose omission issue	0	1	0	5
Product temperature excursion issue	0	1	0	42

Key: EOI=Event(s) of Interest; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term

a: The MedDRA PTs of interest were sorted by decreasing order for the current reporting interval (25 February 2023 to 24 February 2024). A single case may report more than 1 EOI.

b: For the cumulative column, the events were presented in decreasing order based on the event counts of the current reporting interval (25 February 2023 to 24 February 2024).

Of the 9 post-marketing, primary dose cases retrieved during the reporting interval, none of the cases reported the PT of Off-label use. The majority (55.6%; 5/9) of the cases involved medication errors without any additional AEs reported (classified as medication errors without harm); whereas 44.4% (4/9) of cases reported medication errors with harm. These 4 cases reported 38 additional AEs (6 serious; 32 nonserious). The reported events of medication errors in these cases were medication error, overdose, product administration error, and product dose omission issue (n=1 each). The frequency distribution of additional AEs reported in 4 cases reporting medication errors with harm with the use of Ad26.COV2.S is presented in Table 13. Most of the AEs were nonserious and presented local and systemic reactogenicity to Ad26.COV2.S. Serious AEs included headache, herpes zoster, and injection site pain.

Booster Dose

During this reporting interval, a total of 17 (9 medically confirmed and 8 medically unconfirmed) post-marketing, initial cases reported as booster dose were identified. Of these 17 cases, none concerned paediatric patients. These 17 booster cases reported 17 EOI (11 serious; 6 nonserious) of medication errors. Cumulatively, 1,096 (291 medically confirmed and 805medically unconfirmed) post-marketing cases reported as booster dose were identified. Of these 1,096 cases, 7 concerned paediatric patients and are discussed in the subsection below. The remaining 1,089 booster cases reported a total of 1,139 mediation error EOI (32 serious; 1,107 nonserious) and are presented below. An overview of these cases is presented in Table 14.

Table 14: Characteristics of Selected Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Medication Errors

Case Characteristics		Number of Cases Received During the Reporting Interval=17	Number of Cases Received Cumulatively=1,089[a]
Sex	Male	10	512
	Female	6	532
	NR	1	45
Age (Years)[b]	18 to 35	4	218
Minimum: 24	36 to 50	1	268
Maximum: 74	51 to 64	6	188
Mean: 51.1	≥65	3	157
Median: 55	NR	3	248
Sources	Spontaneous	17	765
Country/Territory	Germany	10	39
	United States	3	460
	Philippines	1	3
	Poland	1	1
	Spain	1	5
	United Kingdom	1	1
Classification	Heterologous	14	405
	Homologous	3	684
Event Characteristics		**Number of Events= 17**	**Number of Events= 1,139**
Seriousness (Event Level)[c]	Nonserious	11	1,107
	Serious	6	32
Outcome (Event Level)[c]	NR	17	1,122

Key: EOI=Event(s) of Interest; NR=Not Reported

a: For the cumulative column, the counts were presented in decreasing order based on the current reporting interval (25 February 2023 to 24 February 2024).

b: The median and mean age calculations were based on the current reporting interval (25 February 2023 to 24 February 2024).

c: Seriousness and outcome have been presented for the EOI. A single case may report more than 1 EOI.

Of these 17 post-marketing cases reported as booster dose received during the reporting interval, the most frequently reported country/territory of origin were Germany (n=10), followed by the US (n=3). These cases concerned 6 females, 10 males, and 1 did not report sex. The age range was from 24 to 74 years. The frequency distribution of the MedDRA PTs reported in cases reported as booster is presented in Table 15. A single case may contain more than 1 EOI.

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

MedDRA PTs	Number of Events Reported During the Reporting Interval[a]		Number of Events Reported Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
Interchange of vaccine products	11	3	27	15
Incorrect dose administered	0	3	0	22

Key: EOI=Event(s) of Interest; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term

a: The MedDRA PTs of interest are sorted by decreasing order for the current reporting interval (25 February 2023 to 24 February 2024). A single case may report more than 1 EOI.

b: For the cumulative column, the events were presented in decreasing order based on the event counts of the current reporting interval (25 February 2023 to 24 February 2024).

As displayed in Table 15, the most frequently reported MedDRA PT of interest for this current reporting interval was Interchange of vaccine products (n=14). Of the 17 cases reported as booster dose, the majority (88.2%; 15/17) of them contained additional AEs (classified as medication errors with harm). The frequency distribution of additional AEs (n≥2) reported in these cases is presented in Table 16. 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 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 Interval[a]		Number of Events Received Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
Drug ineffective	10	0	18	0
COVID-19	8	0	16	22
COVID-19 immunisation	0	3	1	9
Gait disturbance	0	2	1	4
Suspected COVID-19	2	0	4	11

Key: AE=Adverse Event; COVID-19=Coronavirus disease 2019; EOI=Event(s) of Interest

a: The AEs with a frequency ≥2 have been presented and sorted by decreasing order for the current reporting interval (25 February 2023 to 24 February 2024). A single case may report more than 1 EOI.

b: For the cumulative column, the events were presented in decreasing order based on the event counts of the current reporting interval (25 February 2023 to 24 February 2024).

Paediatric Cases

Post-marketing Sources (Including Spontaneous and Solicited) Cases

Primary Dose Case

During this reporting interval, a total of 5 medically confirmed (no medically unconfirmed) post-marketing, initial cases reporting medication errors in the paediatric population were retrieved. These 5 cases reported 5 nonserious EOI of medication errors and are presented below. Cumulatively, 377 (199 medically confirmed and 178 medically unconfirmed) post-marketing, primary dose cases reporting medication error EOI in paediatric population were identified. There were 23 serious and 354 nonserious cases which reported a total of 406 medication error events (7 serious; 399 nonserious).

An overview of these cases is presented in Table 17.

Table 17: Characteristics of Selected Cases Involving the Use of Ad26.COV2.S and Reporting Medication Errors

Case Characteristics		Number of Cases Received During the Reporting Interval=5	Number of Cases Received Cumulatively=377[a]
Sex	Male	5	192
Age (Years)[b]	16	3	86
Minimum: 16	17	2	141
Maximum:17			
Mean: 16.4			
Median: 16			
Sources	Spontaneous	5	373
Country/Territory	Portugal	5	12
Event Characteristics		**Number of Events=5**	**Number of Events=406**
Seriousness (Event Level)[c]	Nonserious	5	399
Outcome (Event Level)[c]	Resolved	1	1
	NR	4	404

Key: EOI=Event(s) of Interest; NR=Not Reported

a: For the cumulative column, the counts were presented in decreasing order based on the current reporting interval (25 February 2023 to 24 February 2024).

b: The median and mean age calculation were based on the current reporting interval (25 February 2023 to 24 February 2024). Age group was presented for cases where age was not reported.

c: Seriousness and outcome have been presented for the EOI. A single case may report more than 1 EOI.

All these 5 cases, post-marketing, primary dose, paediatric cases received during the reporting interval were from country of Portugal. All 5 cases concerned male patients. The reported ages were 16 (n=3) and 17 (n=2). The frequency distribution of the MedDRA PTs of interest reported in paediatric cases is presented in Table 18. The most frequently reported medication error PT was Product administered to patient of inappropriate age (n=3).

Table 18: Frequency of MedDRA PTs of Interest in Cases Reporting Medication Errors in the Paediatric Population With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Interval Reporting interval		Number of Events Reported Cumulatively[a]	
	Serious	Nonserious	Serious	Nonserious
Product administered to patient of inappropriate age	0	3	3	345
Product use issue	0	1	0	21
Vaccination error	0	1	0	4

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

a: For the cumulative column, the events were presented in decreasing order based on the event counts of the current reporting interval (25 February 2023 to 24 February 2024).

Paediatric Booster Cases

During this reporting interval, there were no post-marketing, initial cases reported as booster which reported medication error events identified in the paediatric population. 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 7 cases, 1 was serious and 6 were nonserious, which reported a total of 10 EOI (All nonserious) of medication error.

Clinical Trial Cases

During this reporting interval, no primary dose clinical cases and no booster cases reporting medication error were retrieved from Janssen-Sponsored and Janssen-Supported Clinical Studies.

Janssen-Sponsored Clinical Studies

During this reporting interval, no cases reporting medication error related to the use of Ad26.COV2.S were retrieved from a Janssen-Sponsored Clinical Study.

Janssen-Supported Clinical Studies

During this reporting interval, no cases reporting medication error related to the use of Ad26.COV2.S were retrieved from a Janssen-Supported Clinical Study

Line Listings

Death: During the current reporting interval (25February 2023 to 24 February 2024), no fatal cases were retrieved.

MAH Discussion and Conclusion

Overall, the majority of primary dose cases with medication errors involved use of expired product, poor quality product or product that was stored inappropriately. Most of the primary dose cases did not report AEs. Of the booster cases, the majority reported the PT Interchange of vaccine products. Reported AEs in all cases with medication errors usually were nonserious, without evidence for a causal association of AEs to the reported errors. No safety concern arose from review of the paediatric initial and booster cases. 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.

Rapporteur assessment comment:

During the reporting period, medication errors in adults were reported in 14 events related to primary series and 17 events related to booster dose. Most of the cases were related to expired product, poor quality of product and inappropriate storage of the vaccine. The corresponding numbers reported in children vaccinated with Ad26.COV2.S was 5 and 7 respectively.

No new safety concern arises here.

Non-Clinical Data

The following non-clinical study was completed during the reporting interval. The exploratory transcriptomics analysis was considered not suitable and not reliable to explore possible TTS-related pathways based on numerous false positive hits in the huMMR treatment group in the study. Also, evaluation of VITT-related parameters in the same study, such as platelet counts, D-dimer and anti-PF4 and potentially VITT-associated anti-NAP2 antibodies, did not indicate any relevant changes in any of the experimental groups. Therefore, it was opted to not perform transcriptomic analysis of the remaining groups of the study, including the Ad26.COV2.S group.

Table 20: Overview of Completed Non-clinical Study With Focus on TTS for Ad26.COV2.S

Risk	Non-clinical Study Number	Non-clinical Study Title
Thrombosis with thrombocytopenia syndrome	TOX15258	Ad26.COV2.S (Prophylactic COVID-19 Vaccine): A Transcriptomics Exploratory Study in Cambodian Cynomolgus Monkey

Key: Ad26.COV2.S=Adenovirus Type 26 Coronavirus 2 Spike; COVID-19=Coronavirus Disease 2019; TTS=Thrombosis With Thrombocytopenia Syndrome

Rapporteur assessment comment:

No new safety concern was detected here.

Literature

Product-specific Literature

Chang MS, Kim HR, Kim S, et al. Noninfectious Uveitis Risk After COVID-19 Vaccination: A Nationwide Retrospective Cohort Study. Am J Ophthalmol. 2024;258:22-31. doi:10.1016/j.ajo.2023.09.015

Purpose: To investigate the incidence and risk of noninfectious uveitis (NIU) following COVID-19 vaccination compared with an unvaccinated, uninfected control group. *Design:* Retrospective population-based cohort study.
Methods: We included 5,185,153 individuals who received the first vaccine dose in the exposed group and 2,680,164 individuals in the unexposed, uninfected control group. The study observed for 180 days from their index date. Cumulative incidence and risk of NIU following COVID-19 vaccination, and attributable risk factors were assessed.
Results: Multivariable analysis showed elevated risk of nonanterior NIU within 60 days (hazard ratio [HR] 1.27 [95% confidence interval {CI} 1.03-1.55] and 61-180 days (HR 1.39 [95% CI 1.20-1.62]). Subgroup analysis highlighted an increased risk in females for early and delayed nonanterior uveitis (HR 1.44 [95% CI 1.08-1.92]; HR 1.78 [95% CI 1.43-2.20], respectively). Regardless of the location and onset timing of uveitis, a history of NIU was identified as the most significant risk factor, with a high hazard ratio ranging from 100 to 200.
Conclusion: COVID-19 vaccination may modestly increase the risk of nonanterior uveitis especially in females. Despite adjustments, bias may persist in the exposed group, owing to significant differences between unexposed and exposed groups and low incidence of nonanterior uveitis in the unexposed group. Future research should aim to refine these findings by assessing uveitis risk in prior NIU patients and by enlarging the sample size or cohort matching.
Company Comment: A subgroup analysis by vaccine type demonstrated that the highest cumulative incidence of uveitis was associated with the ChAdOX1 vaccine, followed by BNT162b2, mRNA-1273, and Ad26.COV2.S. However, in line with the authors' acknowledgment of potential biases, note is made that at baseline, risk factors for noninfectious uveitis (including but not limited to autoimmune diseases, diabetes mellitus, and recent intraocular surgery) (Rim 2018; Joltikov 2021) were more prevalent in the vaccine-exposed group than controls; these differences were both statistically and clinically significant. Although the study sample was considered by the authors "[...]representative of the entire Korean adult population", it cannot be generalisable to other populations worldwide. Additionally, the GMS data cumulative to 23 January 2024 was retrieved, and analysed the identified 26 cases of iris and uveal tract infections, irritations, and inflammations. No new safety information is detected at this time.

Rapporteur assessment comment:

In this study, a previous history of non-infectious uveitis appeared to be the highest risk factor for developing uveitis again in the future. No new safety concern was identified.

Duijster JW, Schoep ME, Nieboer TE, et al. Menstrual abnormalities after COVID-19 vaccination in the Netherlands: Adescription of spontaneous and longitudinal patient-reported data. Br J Clin Pharmacol. 2023;89(10):3126-3138. doi: 10.1111/bcp.15799

Purpose: During the COVID-19 vaccination campaigns, the number of reports of menstrual abnormalities increased rapidly. Here, we describe the nature and potential risk factors associated with menstrual abnormalities based on spontaneously reporting data as well as data from a prospective cohort event monitoring (CEM) study as these are poorly studied.
Methods: Reports of menstrual abnormalities received by the Netherlands Pharmacovigilance Centre Lareb in the spontaneous reporting system between February 2021 and April 2022 were summarized. In addition, logistic regression analysis was performed on the reported menstrual abnormalities in the CEM study to assess the association between person characteristics, prior SARS-CoV-2 infection and use of hormonal contraceptives and the occurrence of menstrual abnormalities after vaccination.
Results: We analysed over 24 000 spontaneous reports of menstrual abnormalities and over 500 episodes (among 16 929 included women) of menstrual abnormalities in the CEM study. The CEM study showed an incidence of 41.4 per 1000 women aged ≤54 years. Amenorrhoea/oligomenorrhoea and heavy menstrual bleeding collectively accounted for about half of all abnormalities reported. Significant associations were observed for the age group 25-34 years (odds ratio 2.18; 95% confidence interval 1.45-3.41) and the Pfizer vaccine (odds ratio 3.04; 95% confidence interval 2.36-3.93). No association was observed for body mass index and presence of most comorbidities assessed.
Conclusion: The cohort study showed a high incidence of menstrual disorders among women aged ≤54 years, and this observation was supported by the analysis of spontaneous reports. This suggests that a relation between COVID-19 vaccination and menstrual abnormalities is plausible and should be further investigated.
Company Comment: The authors reported that the study identified "the highest" reporting rates for all menstrual

abnormalities together for the Johnson &Johnson vaccine (523.0 per 100,000 vaccinations) stating that "[...]this corresponds to a ratio of1 in 200 female recipients of the Johnson &Johnson vaccine who reported a menstrual abnormality to Lareb". In addition,"[...]over 500 menstrual abnormalities were recorded by participants in the CEM study among 16,929 included women. [...] The incidences of amenorrhoea/oligomenorrhoea and irregular blood loss exceeded 10 per 1000 vaccinated women (aged<65 years) for Johnson & Johnson, Moderna and Pfizer vaccines, while the incidence of heavy menstrual bleeding exceeded 10 per1000 vaccinated women only for the Moderna and Pfizer vaccines." The systemic immune response including hormonal and inflammatory pathways was mentioned by the authors as a potential mechanism. In addition, they also emphasised a different immune activity in the first and second part of the menstrual cycle, stating "[...] most menstrual abnormalities were found in women who were vaccinated in the second part of their menstrual cycle, after ovulation." A signal on "Heavy menstrual bleeding" and "Menstrual cycle and uterine bleeding disorders and postmenopausal haemorrhage" has been previously opened twice but the safety issue was not confirmed. Nevertheless, considering several limitations in both the spontaneous reporting system and the CEM study, lack of detailed data and the analysis that would elucidate the mechanism of these adverse reactions, there is no safety signal identified at this time.

Rapporteur assessment comment:

A signal of heavy menstrual bleeding and menstrual cycle and uterine bleeding disorders and postmenopausal haemorrhage has been opened previously and discussed in relation to this publication. Heavy menstrual bleeding has been considered an ADR for the mRNA vaccines, but not other reproductive bleeding disorders. It is noted that these data do not suggest increase of heavy menstrual bleeding for JCovden. No new safety concern was identified here.

Han JY, Kim S, Han J, et al. Neuro-ophthalmic adverse events of COVID-19 infection and vaccines: A nationwide cohort study. Invest Ophthalmol Vis Sci. 2023;64(14):37. doi: 10.1167/iovs.64.14.37

Purpose: To evaluate the association of COVID-19 infection and vaccination with neuro-ophthalmic adverse events.
Methods: In this nationwide population-based retrospective cohort study, 8,498,353 patients were classified into three groups: control, COVID-19 infection, and COVID-19 vaccination. We conducted separate analyses for the early phase (within 60 days) and late phases (61-180 days) to estimate the incidence rates and hazard ratio (HR) for each neuro-ophthalmic adverse event. The adverse events included in this analysis were optic neuritis, papilledema, ischemic optic neuropathy, third nerve palsy, fourth nerve palsy, sixth nerve palsy, facial palsy, nystagmus, ptosis, blepharospasm, anomalies of pupillary function, and Guillain-Barré syndrome/Miller Fisher syndrome (GBS/MFS).
Results: Neuro-ophthalmic adverse events other than ptosis and GBS/MFS exhibited no significant increase after COVID-19, and their incidence was extremely low. The incidence rate of ptosis in both phases was significantly higher in patients administered COVID-19 vaccination (HR = 1.65 in the early phase and HR = 2.02 in the late phase) than in the control group. Additionally, BNT162b2 conferred a lower ptosis risk than ChAdOx1. GBS/MFS had a significantly higher incidence rate in the early phase (HR = 5.97) in patients with COVID-19 infection than in the control group.
Conclusion: Ptosis was associated with COVID-19 vaccination, particularly with the ChAdOx1 vaccine, while GBS/MFS was associated with COVID-19 infection. In contrast, no association was found between other neuro-ophthalmic adverse events and COVID-19 infection or vaccination. These results may provide helpful insights for diagnosing and treating the neuro-ophthalmological adverse events after COVID-19.
Company Comment: The authors conducted a population-based retrospective cohort study, in which patients were classified into 3 groups: control, COVID-19 infection, and COVID-19 vaccination to identify incidence rate of neuro-ophthalmic adverse events. As mentioned by the authors, "[...]the ChAdOX1 vaccine was strongly associated with ptosis". In the context of the Ad26.COV2.S vaccine, and using the ChAdOx1 vaccine as a reference, Ad26.COV2.S showed a significant negative association with ptosis (HR = 0.41 [95% CI, 0.22 to 0.77]; P = 0.006). Given the negative findings specific to Ad26.COV2.S, no new safety information is detected at this time.

Rapporteur assessment comment:

The aim of this study was to evaluate the association of COVID-19 infection and vaccination with neuro-ophthalmic adverse events, the study was executed in South Korea. Subjects that had received Ad.26.COV2.S constituted the smallest vaccine group (205,008 [4.1%]), for this group none of the outcomes had a hazard ratio with a CI 95% >1. No new safety concern was detected here.

Nahab F, Bayakly R, Sexton ME, et al. Factors associated with stroke after COVID-19 vaccination: a statewide analysis. Front Neurol. 2023 Jun 28;14:1199745. Published 2023 Jun 28. doi:10.3389/fneur.2023.1199745.

Purpose: The objective of our study was to evaluate vaccine type, COVID-19 infection, and their association with stroke soon after COVID-19 vaccination.

Methods: In a retrospective cohort study, we estimated the 21-day post-vaccination incidence of stroke among the recipients of the first dose of a COVID-19 vaccine. We linked the Georgia Immunization Registry with the Georgia Coverdell Acute Stroke Registry and the Georgia State Electronic Notifiable Disease Surveillance System data to assess the relative risk of stroke by the vaccine type.

Results: Approximately 5 million adult Georgians received at least one COVID-19 vaccine between 1 December 2020 and 28 February 2022: 54% received BNT162b2, 41% received mRNA-1273, and 5% received Ad26.COV2.S. Those with concurrent COVID-19 infection within 21 days post-vaccination had an increased risk of ischemic (OR = 8.00, 95% CI: 4.18, 15.31) and hemorrhagic stroke (OR = 5.23, 95% CI: 1.11, 24.64) with no evidence for interaction between the vaccine type and concurrent COVID-19 infection. The 21-day post-vaccination incidence of ischemic stroke was 8.14, 11.14, and 10.48 per 100,000 for BNT162b2, mRNA-1273, and Ad26.COV2.S recipients, respectively. After adjusting for age, race, gender, and COVID-19 infection status, there was a 57% higher risk (OR = 1.57, 95% CI: 1.02, 2.42) for ischemic stroke within 21 days of vaccination associated with the Ad26.COV2.S vaccine compared to BNT162b2; there was no difference in stroke risk between mRNA-1273 and BNT162b2.

Conclusion: Concurrent COVID-19 infection had the strongest association with early ischemic and haemorrhagic stroke after the first dose of COVID-19 vaccination. Although not all determinants of stroke, particularly comorbidities, were considered in this analysis, the Ad26.COV2.S vaccine was associated with a higher risk of early post-vaccination ischemic stroke than BNT162b2.

Company Comments: According to the study results, "the 21-day post-vaccination incidence of ischaemic stroke was 8.14, 11.14, and 10.48 per 100,000 for BNT162b2, mRNA-1273 and Ad26.COV2.S recipients, respectively. After adjusting for age, race, gender, and COVID-19 infection status there was a 57% higher risk (OR=1.57, 95% CI: 1.02, 2.42) for ischaemic stroke within 21 days of vaccination associated with the Ad26.COV2.S vaccine compared to BNT162b2." The authors indicated that "concurrent COVID-19 infection had the strongest association with early ischaemic and haemorrhagic stroke after first dose COVID-19 vaccination", though with no evidence for interaction between vaccine type. "The Ad26.COV2.S vaccine was associated with a higher risk of early post-vaccination ischaemic stroke than BNT162b2." No information on patients' comorbidities, concomitant medications, examination and diagnostic details were presented in the study. Among the limitations, retrospective nature of the study and the increased use of home COVID-19 tests that may contribute to an underreporting of COVID-19 infection as well as unavailable data to determine if any of these early post-vaccination strokes were related to thrombotic thrombocytopaenia. Hence, given the limited information, there is no new safety information detected at this time.

Rapporteur assessment comment:

In this retrospective cohort study, the 21-day post-vaccination incidence of stroke among the recipients of the first dose of a COVID-19 vaccine (mRNA or Ad26.COV2.S) was evaluated. The authors concluded that concurrent covid-19 infection had the strongest association with early ischemic and haemorrhagic stroke after the first dose of COVID-19 vaccination and that there was a higher risk associated with Ad26.COV2.S than BNT162b2. As the MAH pointed out, comorbidities were not considered in the analysis.

TTS, venous thromboembolism and ITP are already included in the SmPC section 4.4 and 4.8. No additional safety information was noted here.

Class Effect Literature

Yoo H, Kim SY, Park MS, et al. COVID-19 Vaccine-Associated Pneumonitis in the Republic of Korea: A Nationwide Multicenter Survey. J Korean Med Sci. 2023;38(14):e106. Published 2023 Apr 10. doi:10.3346/jkms.2023.38.e106.

Recent reports have suggested that pneumonitis is a rare complication following vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). However, its clinical features and outcomes are not well known. The aim of this study was to identify the clinical characteristics and outcomes of patients with vaccine-associated pneumonitis following vaccination against SARS-CoV-2.

Methods: In this nationwide multicenter survey study, questionnaires were distributed to pulmonary physicians in referral hospitals. They were asked to report cases of development or exacerbation of interstitial lung disease (ILD) associated with the coronavirus disease 2019 vaccine. Vaccine-associated pneumonitis was defined as new pulmonary infiltrates documented on chest computed tomography within 4 weeks of vaccination and exclusion of other possible etiologies.

Results: From the survey, 49 cases of vaccine-associated pneumonitis were identified between February 27 and October 30, 2021. After multidisciplinary discussion, 46 cases were analyzed. The median age was 66 years and 28 (61%) were male. The median interval between vaccination and respiratory symptoms was 5days. There were 20 (43%), 17 (37%), and nine (19%) patients with newly identified pneumonitis, exacerbation of pre-diagnosed ILD, and undetermined pre-existing ILD, respectively. The administered vaccines were BNT162b2 and ChAdOx1 nCov-19/AZD1222 each in 21 patients followed by mRNA-1273 in three, and Ad26.COV2.S in one patient. Except for five patients with mild disease, 41 (89%) patients were treated with corticosteroid. Significant improvement was observed in 26 (57%) patients including four patients who did not receive treatment. However, ILD aggravated in 9 (20%) patients despite treatment. Mortality was observed in eight (17%) patients.

Conclusion: These results suggest pneumonitis as a potentially significant safety concern for vaccines against SARS-CoV-2. Clinical awareness and patient education are necessary for early recognition and prompt management. Additional research is warranted to identify the epidemiology and characterize the pathophysiology of vaccine-associated pneumonitis.

Company Comment: According to the study results, "There were 20 (43%), 17 (37%), and 9 (19%) patients with newly identified pneumonitis, exacerbation of pre-diagnosed ILD, and undetermined pre-existing ILD, respectively. The administered vaccines were BNT162b2 and ChAdOx1 nCov-19/AZD1222 each in 21 patients followed by mRNA-1273 in 3 and Ad26.COV2.S in 1 patient. Half of the patients (54%) experienced development or exacerbation of ILD after the first dose of vaccination." The authors mentioned that there were no significant differences in clinical characteristics and outcomes between patients who received mRNA vaccines and vector-based vaccines. Of the seven deceased patients, "pneumonitis occurred in one patient after the second dose of ChAdOx1 nCov-19 and the patient died of respiratory failure due to the progression of pneumonitis." Two patients with pre-diagnosed ILD experienced an exacerbation of ILD following the second dose of BNT162b2 leading to respiratory failure. Vaccination with the second dose of ChAdOx1 nCov-19/AZD1222 led to exacerbation of ILD in a patient and the patient died from hospital-acquired pneumonia. In other 3 deceased patients who received the second dose of ChAdOx1 nCov-19, the death occurred from "hospital-acquired pneumonia, sepsis or intracranial haemorrhage." Among the potential mechanisms of pneumonitis associated with the COVID-19 vaccine, the authors discussed "immune-mediated injuries, especially T cell-mediated reactions" as well as "vaccine-induced autoimmunity". Nevertheless, taking into consideration the study limitations, such as "no single confirmative test for the diagnosis of vaccine-associated pneumonitis", the frequency of the vaccines used at the timepoint (BNT162b2 was the most administered followed by ChAdOx1 nCov-19), potential selection bias including only severe cases, not generalisability of the study population limited to the Korea ILD Study Group, retrospective nature of the study including limited COVID infection testing as well as the possibility of underestimation of vaccine-associated pneumonitis by limiting the time interval to 4 weeks especially "if potential pathophysiology is due to autoimmunity", there is no new safety information identified at this time.

Rapporteur assessment comment:

This survey executed in South Korea including answers from 21 hospitals, with the aim to identify the clinical characteristics and outcomes of patients with vaccine-associated pneumonitis following vaccination against SARS-CoV-2. Only one of the 49 reported subject had received Ad26.COV2.S. It is noted that the definition includes new symptoms or worsening of preexisting symptoms within 4 weeks of administration and that there are several limitations such as study design. No new safety concern is detected here.

Other Periodic Reports

This section is not applicable as no other COVID-19 vaccine PBRERs concerning Ad26.COV2.S have been prepared

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 Concerns/ Variants Of Interest (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 the 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]: 58.9% [43.40; 70.50] 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 (<37%). 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 61% 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 remain 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 data regarding effectiveness against omicron variants has been presented.

1.3.7. Late-breaking information

Since the DLD of 24 February 2024, no late-breaking information has been identified regarding Ad26.COV2.S.

2. Signal and risk evaluation

2.1. Summary of safety concerns

At the Beginning of the Reporting Interval

The summary of safety concerns (ie, important identified risks, important potential risks, and missing information) at the beginning of the reporting interval to be included in the Ad26.COV2.S PBRER are based on cRMP (version 6.0, dated 25October 2022) and are summarised in Table 44. 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 5.3 (dated 13 February 2023) 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 44: Important Identified Risks, Important Potential Risks, and Missing Information at the Beginning of the Reporting Interval

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

a: Immune thrombocytopenia is characterised in the European Union Risk Management Plan, version 5.3, as an important identified risk "Thrombocytopenia, including immune thrombocytopenia."

At the End of the Reporting Interval

During the reporting interval, the safety concerns were re-evaluated as follows:

The cRMP version 6.0 was updated to version 7.0 on 10 May 2023 with the addition of the important identified risk of "Myocarditis and pericarditis".

The cRMP version 7.0 was updated to version 8.0 on 06 February 2024 with the removal of the missing information "Interaction with other vaccines" and reclassification of the important potential risk "Immune thrombocytopenia" to an important identified risk with renaming to "Thrombocytopenia, including immune thrombocytopenia."

The EU-RMP version 5.3 was updated to version 7.1 on 13 June 2023.
The updated summary of safety concerns is presented in Table 45.

Table 45: Important Identified Risks, Important Potential Risks, and Missing Information at the End of the Reporting Interval

Important Identified Risks	Thrombosis with thrombocytopenia syndrome Guillain-Barré syndrome Venous thromboembolism Myocarditis and pericarditis Thrombocytopenia, including immune thrombocytopenia
Important Potential Risks	Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD)
Missing Information	Use during pregnancy Use in breastfeeding women Use in immunocompromised patients Use in patients with autoimmune or inflammatory disorders Interaction with other vaccines[a] Use in frail patients with comorbidities (eg, chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders) Long-term safety

Key: EU-RMP=European Union Risk Management Plan
a: EU-RMP only

Rapporteur assessment comment:

During the reporting interval, "Myocarditis and pericarditis" was added as an important identified risk. Furthermore, "Interaction with other vaccines" was removed from missing information and the important potential risk "Immune thrombocytopenia" was reclassified to an important identified risk with renaming to "Thrombocytopenia, including immune thrombocytopenia."

2.2. Signal evaluation

2.2.1. Ongoing or Closed Signals

Tabular overview of signals: ongoing or closed during the reporting interval. There were no signals that were undergoing evaluation at data-lock date of this report.

Signal Term	Date Detected DD/MMM/YYYY	Status (Ongoing or Closed)	Date Closed (for Closed Signals) DD/MMM/YYYY	Source or Trigger of Signal	Reason for Evaluation and Summary of Key Data	Method of Signal Evaluation	Action(s) Taken or Planned
Cerebral haemorrhage	12/Dec/2022	CLOSED/SAFETY ISSUE NOT-CONFIRMED	20/Jul/2023	Internal Signal Detection - Company Database - Single case assessment	This topic has been reviewed by the Company in the past. New information has been received that warrants a new review of this topic. On 12DEC2022 a signal was identified for Cerebral haemorrhage, with the use of COVID-19 VACCINE AD26.COV2.S during a single case assessment.This signal was reassessed due to the association of events with fatal outcomes/serious medical consequences, the association with permanent disability/sequelae, the impact of the events on patient quality of life, the potential of the event to alter the benefit-risk profile, and the fact that is a safety topic with regulatory interest. This signal was reassessed because this is an unlisted event, due to the fact that this is a preventable event, due to the significant case volume, based on the statistical association between the drug and the event, and based on the temporal association of the events.	"The evaluation method included a cumulative case series review of available data in the Global Safety Database through 24FEB2023 (n=959 primary dose and 42 booster dose cases) reporting the Preferred Terms from the Medical Dictionary for Regulatory Activities (MedDRA) Standardised MedDRA Query: haemorrhagic central nervous system vascular conditions.	Inclusion in Periodic Benefit Risk Evaluation Report.
Heavy menstrual bleeding	17/Jan/2023	CLOSED/SAFETY ISSUE NOT-CONFIRMED	20/Jul/2023	Internal Signal Detection - Company Database - Aggregate	This topic has been reviewed by the Company in the past. New information has been received that warrants a new review of this topic. On 17JAN2023 a signal was identified for the event Heavy menstrual bleeding, with the use of COVID-19 VACCINE AD26.COV2.S based on a statistical signal of disproportionate reporting identified within the Company Global Safety Database. This signal was reassessed due to the impact of the events on patient quality of life, because this is an unlisted event, due to the need to notify patients of need for prompt medical attention when bleeding is severe, due to the significant case volume, due to the appearance of	The evaluation method included a cumulative case series review of available data in the Global Safety Database through 24FEB2023 (n=1190 primary dose and 41 booster dose cases) reporting the following Medical Dictionary for Regulatory Activities Preferred Terms: Heavy menstrual bleeding, Menometrorrhagia, and Polymenorrhagia. Data mining analysis of the Food and Drug Administration Vaccine Adverse Event Reporting System, EudraVigilance, and World Health Organization VigiBase was	Routine Pharmacovigilance Activities

					similar findings in multiple data sources, based on the statistical association between the drug and the event, and based on the temporal association of the events.	performed. A review of relevant preclinical data, a review of relevant scientific literature and an analysis of relevant clinical trial data was conducted.	
Myocarditis and Pericarditis	14/Feb/2023	CLOSED/SAFETY ISSUE CONFIRMED	28/Mar/2023	Health Authority	This topic has been reviewed by the Company in the past. New information has been received that warrants a new review of this topic. On 14FEB2023 a signal was identified for Cardiac inflammatory disease (including Myocarditis and Pericarditis) with the use of COVID-19 VACCINE AD26.COV2.S based on a request from the United States Food and Drug Administration to perform a review of the topic. This signal was reassessed because it is a safety topic with regulatory interest.	The evaluation method included a cumulative case series review of available data in the Global Safety Database through 24FEB2023 (n=436 cases; Post authorization sources) reporting the Preferred Terms from the Medical Dictionary for Regulatory Activities High-Level Terms: Noninfectious myocarditis and Noninfectious pericarditis. Data mining analysis of the Food and Drug Administration Vaccine Adverse Event Reporting System, EudraVigilance, and World Health	Change to Reference Safety Information /Labeling: Company Core Data Sheet update, change to local labeling/package insert, Investigator's Brochure update, update to patient information. Risk Management Plan (RMP) Update: Important Identified Risk,
						Organization VigiBase was performed. Analysis of relevant clinical trial data, analysis of relevant data from observational databases, a calculation of reporting rates of the events, a drug-class labeling comparison, a review of relevant preclinical data, a review of relevant scientific literature, and a trending analysis of the events was performed.	Pharmacovigilance Plan.; Inclusion in the Periodic Benefit Risk Evaluation Report.
Postural Orthostatic Tachycardia Syndrome	22/Feb/2023	CLOSED/SAFETY ISSUE NOT-CONFIRMED	04/Apr/2023	Health Authority - PBRER/PSUR Assessment Report (eg PRAC), Internal Signal Detection - Company Database - Aggregate, Literature	On 22FEB2023 a signal was identified for the event of Postural Orthostatic Tachycardia Syndrome (POTS) with the use of COVID-19 VACCINE AD26.COV2.S based on data mining analysis that showed disproportionality. In addition, preliminary analysis of literature has shown possible interaction between the Spike component of the vaccine and angiotensin-	The evaluation method included a cumulative case series review of available data in the Global Safety Database through 24FEB2023 (n=64 cases) reporting the following Medical Dictionary for Regulatory Activities Preferred Terms (PTs): Postural Orthostatic Tachycardia Syndrome, Dizziness	Inclusion in the Periodic Benefit Risk Evaluation Report.

					converting enzyme 2 which could provide a plausible mechanism of action. This signal was created due to the fact that is a safety topic with regulatory interest, due to disproportionate reporting of the term, due to biological plausibility, and based on the statistical association between the drug and the event.	postural, and Postural reflex impairment. Cumulatively till the Data Lock Point, a total of 22 cases under the PT Postural Orthostatic Tachycardia Syndrom" and 42 cases under the PT Dizziness postural were received by the Company. There were no cases under the PT Postural reflex impairment. Data mining analysis of the Food and Drug Administration Vaccine Adverse Event Reporting System, EudraVigilance, and World Health Organization VigiBase was performed. Analysis of relevant clinical trial data, a review of relevant preclinical data, and a review of relevant scientific literature was performed.	
Appetite disorders	15/Mar/2023	NEW SIGNAL; CLOSED/SAFETY ISSUE NOT-CONFIRMED	04/May/2023	Health Authority	On 15MAR2023 a signal was identified for Appetite disorders with the use of COVID-19 VACCINE AD26.COV2.S based on a request from Ghana Food and Drugs Authority. This signal was created because it is a safety topic with regulatory interest.	The evaluation method included a cumulative case series review of available data in the Global Safety Database through 24FEB2023 (n= 1,263 primary dose cases, 38 booster cases) reporting the following Medical Dictionary for Regulatory Activities High-Level Term: Appetite disorders. Data mining analysis of the Food and Drug Administration Vaccine Adverse Event Reporting System, EudraVigilance, and World Health Organization VigiBase was performed. A review of relevant clinical trial data and a review of relevant scientific literature was performed.	Routine pharmacovigilance activities
Encephalitis including Acute Disseminated	17/Oct/2023	NEW SIGNAL; CLOSED/SAFETY ISSUE	18/Dec/2023	Internal Signal Detection - Company	This topic has been reviewed by the Company in the past. New information has	The evaluation method included a cumulative case series review of	Ongoing PV Monitoring Activities field:

Encephalomyelitis		NOT-CONFIRMED		Database - Aggregate, Internal Signal Detection - Company Database - Single case assessment, Internal Signal Detection - Food and Drug Administration Vaccine Adverse Event Reporting System, Internal Signal Detection - World Health Organization VigiBase	been received that warrants a new review of this topic. On 17OCT2023 a signal was identified for the event of Encephalitis including Acute Disseminated Encephalomyelitis with the use of COVID-19 VACCINE AD26.COV2.S based on routine signal detection activities (Individual Case Safety Report review of Adverse Event(s) of Special Interests and data mining). This signal was created due to the association of events with fatal outcomes/serious medical consequences, due to the percentage of serious cases, due to biological plausibility and based on the statistical association between the drug and the event.	available data in the Global Safety Database through 24AUG2023 (n=102 cases (all case types) reporting the following Medical Dictionary for Regulatory Activities (MedDRA) Standardized MedDRA Query: Noninfectious encephalitis (narrow). Data mining analysis of the Food and Drug Administration Vaccine Adverse Event Reporting System, the Food and Drug Administration Adverse Event Reporting System, EudraVigilance, and World Health Organization VigiBase was performed. An analysis of relevant clinical trial data, a drug-class labeling comparison, a review of relevant scientific literature, a review of Real World Evidence	Routine Pharmacovigilance Activities, Inclusion in Periodic Benefit Risk Evaluation Report. The topic is being closely monitored as an Adverse Event of Special Interest.

Key: Apr=April; COVID-19=Coronavirus Disease 2019; Dec=December; Feb=February; Inc.=Including; Jan=January; Jul=July; Mar=March; MedDRA=Medical Dictionary for Regulatory Activities; n=Number; Oct=October; PBRER/PSUR=Periodic Benefit Risk Evaluation Report/ Periodic Safety Update Report; POTS=Postural Orthostatic Tachycardia Syndrome; PRAC=Pharmacovigilance Risk Assessment Committee; PSUR=Periodic Safety Update Report; PT=Preferred Terms; PV=Pharmacovigilance; RMP=Risk management Plan; SMQ=Standardised Medical Dictionary for Regulatory Activities Queries; WHO=World Health Organisation

Rapporteur assessment comment:

During the reporting interval the following signals were closed: Cerebral haemorrhage (not confirmed), heavy menstrual bleeding (not confirmed), myocarditis and pericarditis (confirmed), postural orthostatic tachycardia syndrome (not confirmed), appetite disorders (not confirmed) and encephalitis including acute disseminated encephalomyelitis (not confirmed).

There were no signals that were undergoing evaluation at data-lock date of this report.

2.2.1.1. Closed Signals

Cerebral Haemorrhage

Request: On 12 December 2022, a signal was identified based on a single case review for cerebral haemorrhage with the use of JCOVDEN® (Ad26.COV2.S). This topic has been reviewed by the Company in the past on 22 October 2020. New information has been received that warrants a new review of this topic. This signal was reassessed due to the association of events with fatal outcomes/serious medical consequences, the association with permanent disability/sequelae, the impact of the events on patient quality of life, the potential of the event to alter the benefit-risk profile, and the fact that is a safety topic with regulatory interest. This signal is also an unlisted event, due to the fact that this is a preventable event, due to the significant case volume, based on the statistical association between the drug and the event, and based on the temporal association of the events. The validation method included an interval case series review of relevant data in the Company global safety database from 25February 2022 through 24 August 2022.

Table 7: Case counts and disproportionality scores for cerebral hemorrhage events and Janssen COVID-19 Vaccine in VigiBase through 4 quarter 2022 (MedDRA terms with ≥3 cumulative cases)

MedDRA Terms	N	EBGM	EB05
Custom term with 26 PTs suggestive of cerebral hemorrhage	309	1.82	1.66
Cerebral haemorrhage	**186**	**2.24**	**1.98**
Subarachnoid haemorrhage	**51**	**2.24**	**1.77**
Haemorrhagic stroke	**34**	**2.28**	**1.71**
Subdural haematoma	23	1.39	0.98
Haemorrhage intracranial	16	0.95	0.62
Cerebral haematoma	14	1.86	1.18

JCOVDEN (Ad26. COV2.S)
Primary Cerebral Haemorrhage

Table 7: Case counts and disproportionality scores for cerebral hemorrhage events and Janssen COVID-19 Vaccine in VigiBase through 4 quarter 2022 (MedDRA terms with ≥3 cumulative cases)

MedDRA Terms	N	EBGM	EB05
Intraventricular haemorrhage	**9**	**2.05**	**1.17**
Haemorrhagic transformation stroke	6	1.86	0.94
Basal ganglia haemorrhage	5	1.97	0.94

Note 1: All PTs with at least one case shown. **Bolded = Score is disproportionately reported.**
Note 2: Vaccine-event combinations may not be included in the results, if not retrieved within VAERS.
Key: EB05= Lower bound of the 90% confidence interval; EB95= Upper bound of the 90% confidence interval; EBGM=Empirical Bayesian Geometric Mean; FAERS=FDA Adverse Event Reporting System; FDA=Food and Drug Administration; N=number; PT=Preferred term
Threshold: The statistical threshold for disproportionality for a drug-event combination is EBGM of ≥2, a EB05 >1, and N ≥3.

Table 8: Case counts and disproportionality scores for cerebral hemorrhage events and COVID-19 (Janssen) in VAERS through 23-Sep-2022 (MedDRA PTs with ≥3 cumulative cases)

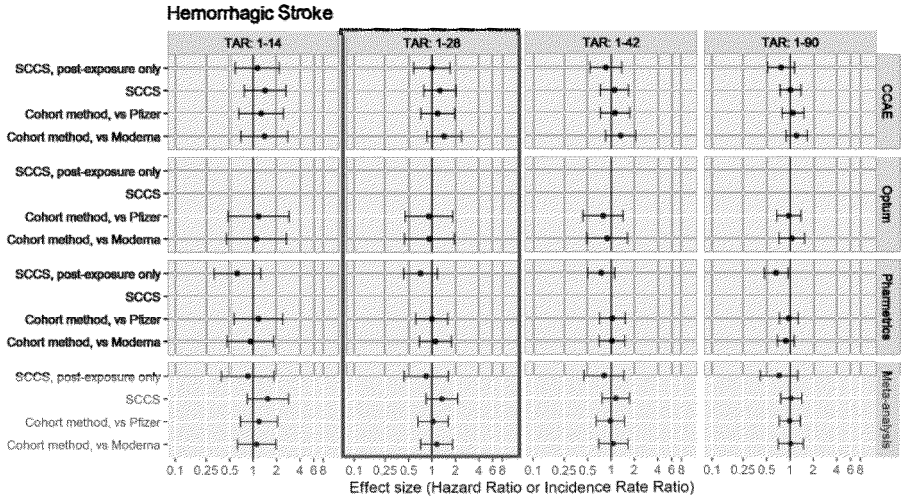
MedDRA Terms	N	Disprop	Disprop 025
Custom term with 26 PTs suggestive of cerebral hemorrhage	163	2.68	2.24
Cerebral haemorrhage	93	3.31	2.61
Subarachnoid haemorrhage	26	2.64	1.68
Haemorrhagic stroke	18	2.86	1.65
Subdural haematoma	18	2.00	1.15
Haemorrhage intracranial	8	1.23	0.53
Haemorrhagic transformation stroke	7	5.24	2.12
Cerebral haematoma	6	3.35	1.26
Intraventricular haemorrhage	6	2.37	0.89
Basal ganglia haemorrhage	5	3.26	1.10
Brain stem haemorrhage	3	2.68	0.64

JCOVDEN (Ad26. COV2.S)
Primary Cerebral Haemorrhage

Table 8: Case counts and disproportionality scores for cerebral hemorrhage events and COVID-19 (Janssen) in VAERS through 23-Sep-2022 (MedDRA PTs with ≥3 cumulative cases)

Note 1: Preferred Terms with ≥3 cumulative cases are shown. Bolded = Score is disproportionately reported.
Note 2: Vaccine-event combinations may not be included in the results, if not retrieved within VAERS.
Threshold: The statistical threshold for disproportionality for a drug-event combination is Disprop >2, Disprop 025 >1 and N ≥3.
Key: Disprop=Semi-Empirical Information Component, a modified version of the disproportionality statistic developed by the World Health Organization; Disprop 025=Lower bound of the 95% confidence interval for the Semi-Empirical Information Component; VAERS=FDA Vaccine Adverse Event Reporting System; FDA=Food and Drug Administration; N=number

Figure 1: Rapid Cycle Analysis Results for Cerebral Hemorrhage, May 2023



Key: SCCS=Self-Controlled Case Series, TAR=Time-at-Risk; vs=Versus

The search of the GMS global safety database retrieved 959 primary dose cases and 42 booster dose cases from the SMQ Haemorrhagic central nervous system vascular conditions in patients who received AD26.COV2.S. The distribution of the PTs of interest is presented in Table 12 for the 128 primary dose cases of interest identified for further review and in Table 13 for the 7 booster dose cases of interest identified for further review.

Of the 959 primary dose cases identified by the search, 831 cases were deferred by case screening from detailed review for the reasons outlined in Table 16.

Of the 42 booster dose cases identified by the search, 35 cases were deferred by case screening from detailed review for the reasons outlined in Table 17.

Table 16: Disposition of Cases Reporting Events Related to Haemorrhagic Central Nervous System Vascular Conditions With Primary Dose Vaccination of Ad26.COV2.S (n=959)

Case Subset	Number of Cases
All Cases	**959**
Cases Not Meeting Case Definition	**831**
Cases not meeting search criteria/no cases identified through STeMS search	722[a]
Cases included on TTS tracker	59[a]
Cases reporting ITP	14[b]
Case where patient was not exposed to Ad26.COV2.S vaccine	13[c]
Cases reporting trauma to head	7[d]
Cases concurrent with thrombotic event and likely not a primary cerebral haemorrhage	6[e]
Cases reporting haemorrhagic transformation stroke	6[f]
Cases reporting multiple patients	3[g]
Duplicate case - deleted from database	1[h]
Selected Cases for Detailed Review (eg, Cases Meeting Case Definition)	**128**
Cases with confounding medical history/concurrent conditions/cosuspect or concomitant medications/concurrent events	46[a]
Cases not meeting the risk window	40[a]
Cases reporting limited information for a meaningful medical assessment	36[a]
Cases included for detailed review	5[i]
Case reported in neonate	1[j]

Table 16: **Disposition of Cases Reporting Events Related to Haemorrhagic Central Nervous System Vascular Conditions With Primary Dose Vaccination of Ad26.COV2.S (n=959)**

Key: Ad26.COV2.S=Coronavirus Disease 2019 Vaccine Janssen; ITP=Immune thrombocytopenia; n=Number of Cases; STeMS=Self-service Text Mining Solution; TTS=Thrombosis with Thrombocytopenia Syndrome

a: Please refer to Attachment 2 for AER#s.

b: [redacted]

c:

d:

e:

f:

g:

h:

i:

j:

Table 17: **Disposition of Cases Reporting Events Related to Haemorrhagic Central Nervous System Vascular Conditions With Booster Dose Vaccination of Ad26.COV2.S (n=959)**

Case Subset	Number of Cases
All Cases	**42**
Cases not meeting search criteria/no cases identified through STeMS search	34[a]
Case included on TTS tracker	1[b]
Cases included for detailed review	**7**
Cases not meeting the risk window	4[c]
Cases with confounding medical history/concurrent conditions/cosuspect or concomitant medication/concurrent event	1[d]
Cases included for detailed review	2[e]

Key: AER#s=Adverse Event Report Numbers; n=Number of Cases; STeMS=Self-service Text Mining Solution; TTS=Thrombosis With Thrombocytopenia Syndrome.

a: Please refer to Attachment 3 for AER#s.

b: [redacted]

c:

d:

e:

Cases that are not confounded and included adequate information involving patients ≥50 years of age were presented by the MAH with narrative summaries. All cases involving patients <50 years of age, including the case involving the neonatal patient, are presented, regardless of risk window, confounding factors, or information available.

Of the 37 cases with hemorrhagic events after the first vaccination, 32 involved patients who were <50 years of age. Of these cases, 10 were outside the risk window, 12 were confounded (the most frequently reported confounders were hypertension (6), obesity (5), and diabetes (3)), 9 provided limited information, and 1 was a neonatal case. The remaining 5 cases involved patients who were ≥50 years of age. Of these cases, all occurred within the risk window, none were confounded, and all provided enough information to make a meaningful medical assessment.

Of the 4 cases with hemorrhagic events after booster, all involved patients who were <50 years of age. Of these cases, 2 were outside the risk window. Neither were confounded and both provided enough information to make a meaningful medical assessment. Of the remaining 2 cases, both occurred within the risk window, neither were confounded, and both provided enough information to make a meaningful medical assessment.

MAH Conclusion: Based on this review, there was insufficient evidence to suggest a reasonable possibility that cerebral haemorrhage is causally associated with Ad26.COV2.S vaccine. Key factors supporting this conclusion include:

1. no imbalance in reporting rate of SMQ "Haemorrhagic CNS vascular conditions" was observed during the double-blind phase of the primary pooled analysis

2. insufficient evidence regarding the causal role of the Ad26.COV2.S vaccine and cerebral haemorrhage based on the review of post-marketing data

3. RWE Rapid Cycle analysis indicated lack of evidence of increased risk of cerebral haemorrhage with Ad26.COV2.S

4. although different Mechanism Of Action (MOA) were proposed in the literature, no MOA has been identified yet for the development of cerebral haemorrhage in association with adenoviral vector COVID-19 vaccines

Three out of 4 databases used in the data mining analysis reported disproportionately for cerebral haemorrhage. The restricted haemorrhagic stroke O/E sensitivity analysis for the 1 to 28 days risk window (the established risk window for haemorrhagic stroke) also revealed statistically significant O/E ratios >1 for nearly all female and male age groups for the US and for female 18 to 29 years and 40 to 49 years age groups and male 18 to 29 years and 30 to 39 years age groups for the EU. However, although some imbalances are reported, further detailed review of the post-marketing data used in these analyses showed that the cases occurred outside the risk window, were confounded, or did not provide enough information to make a meaningful medical assessment.

Rapporteur assessment comment:

The company presents a comprehensive cumulative analysis of haemorrhage based on several sources. 3 out of 4 databases reported disbalances: A slight imbalance is seen for a custom term composed of 26 terms based on cases seen without rivaroxaban treatment in the company's database (BCPNN >2 with BCPNN 025 >= 1). Some of the PTs met threshold for disproportionality in VigiBAse, namely Cerebral haemorrhage (2.25), Subarachnoid haemorrhage (2.25), Haemorrhagic stroke (2.28), and Intraventricular haemorrhage (2.05). In the VAERS database, the custom term (2.26) as well as several individual PTs met statistical threshold for disproportionality. These include Cerebral haemorrhage (3.31), Subarachnoid haemorrhage (2.64), Haemorrhagic stroke (2.86), Subdural haematoma (2), Haemorrhagic transformation stroke (5.24), Cerebral haematoma (3.35), and Basal ganglia haemorrhage (3.26). None of the 26 PTs within the Haemorrhagic central nervous system vascular conditions (SMQ; Narrow) met the statistical threshold for disproportionality in EudraVigilance. Overall disproportionalities are partly seen in the different databases as also observed before.

Real world Evidence Rapid cycle analysis showed for the 1 to 28 day TAR following the first Ad26.COV2.S dose, that there is a lack of evidence of increased risk for hemorrhagic stroke. In separate sex and age (18-59 and 60+ years) stratified analyses, there was no evidence of increased risk of hemorrhagic stroke for any group.

Narrative analysis does in only a very few cases may allow to conclude on a plausible relationship based on a reasonable time frame of < 28 days and lacking strong other confounders.

Overall, the view can be endorsed that no new safety concern is detected here.

Heavy Menstrual Bleeding

On 17 January 2023 a signal was identified for the event Heavy menstrual bleeding, with the use of Ad26.COV2.S based on a statistical signal of disproportionate reporting identified within the Company global safety database.

MAH Conclusion: Based on this review, the cumulative weight of evidence does not suggest a reasonable possibility that Ad26.COV2.S is directly associated with Heavy Menstrual bleeding. Key factors supporting

this conclusion include: No imbalances observed for heavy menstrual bleeding during the double-blind phase clinical trials. Disproportionate reporting was driven from stimulated reporting from the Netherlands, previously evaluated by the Company.

Rapporteur assessment comment:

A signal of heavy menstrual bleeding and menstrual cycle and uterine bleeding disorders and postmenopausal haemorrhage has been opened previously and discussed in relation to this publication. Heavy menstrual bleeding has been considered an ADR for the mRNA vaccines, but not other reproductive bleeding disorders.

The MAH has provided a comprehensive review of different bleeding events (see submitted PSUR), where also heavy menstrual bleeding was addressed. Overall, no clear support for causality was identified based on these data. Overall, the MAH's conclusion is agreed.

Postural Orthostatic Tachycardia Syndrome

Request: In the second updated Pharmacovigilance Risk Assessment Committee Rapporteur Assessment report (PRAC AR) (PRAC AR Ad26.COV2.S 2023), (procedure number: EU EMEA/H/C/PSUSA/00010916/202208) for the third Ad26.COV2.S PBRER (reporting interval 25February 2022 to 24 August 2022), circulated on 04 April 2023, the EMA requested the following:
"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."

Methods:

Methods included Datamining (disproportionality analysis), cumulative review of cases reporting POTS and/or Postural dizziness or Postural reflex impairment with the use of Ad26.COV2.S from the Global Medical Safety (GMS) global safety database, Observed-versus-expected analysis and review of literature data.

Results:

Datamining

As the GMS global safety database did not contain cases with postural reflex impairment the analysis was performed using the MedDRA PTs of Postural orthostatic tachycardia syndrome and Dizziness postural only (in combination as custom term, or individually). Data mining was performed using 4 databases (GMS global safety database, EudraVigilance, WHO Vigibase and FDA VAERS.

Overall, results were not consistent across databases and across terms. Only the individual MedDRA PT Postural orthostatic tachycardia syndrome met the statistical threshold for disproportionality in both the GMS global safety database and EudraVigilance, but not in the WHO VigiBase or FDA VAERS databases.

Review of cases from the GMS global safety database. Sixty-four cases were identified in the database with events coded to the MedDRA PTs of Postural Orthostatic Tachycardia syndrome or Dizziness Postural. There were no case reports of Postural Reflex Impairment. Two of the 22 cases reporting POTS met the case definition for POTS, and both cases contained risk/contributing factors for the condition (positive Borellia test or autoimmune thyroiditis). In a further eight cases the diagnostic criteria for POTS were not met, and four of these cases documented alternative etiologies for tachycardia including Guillain-Barré syndrome, bipolar manic episodes, dehydration, or active bleeding for an extended period of time (underlying and concurrent menometrorrhagia and associated bicytopenia). In addition, 2 of the 8 cases reported long COVID-19/sequellae of COVID-19. Eleven of the 22 cases contained insufficient information to establish "fully met", "partially met" or "did not meet" diagnostic criteria for POTS. In seven of these cases the patient had associated co-morbidities or alternative etiologies that could have contributed to the reported events, including Ehlers-Danlos syndrome and/or pre-existing POTS (n=2), history ofCOVID-

19/post COVID-19 syndrome (n=2), Sjogren's syndrome (n=1), a medical history of atrioventricular nodal re-entrant tachycardia (n=1) or concurrent Epstein-Barr virus reactivation and mast cell activation syndrome (n=1). The remaining case referred to the Kwan et al publication (Kwan 2022). Only 2 of the 42 cases with dizziness postural co-reported tachycardia/increased heart rate which either occurred in the context of reactogenic manifestations including fever or in association with pulmonary embolism. Based on review of the 42 cases with dizziness postural, there was no indication that the event would represent a manifestation of POTS.

Review of literature

Review of the literature revealed 1 citation deemed relevant to the research question (Kwan 2022). Data from the study indicated that, in a cohort of 284,592 COVID-19-vaccinated individuals using a sequence–symmetry analysis, the odds of POTS were higher 90 days after vaccine exposure than 90 days before exposure. It was also shown that the odds for POTS were higher than referent conventional primary care diagnoses but lower than the odds of new POTS diagnosis after SARS-CoV-2 infection.
The MAH's assessment of the Kwan study indicated that further analyses would be needed to validate the results of this publication. The study provided a preliminary but non-specific signal regarding POTS and COVID-19 vaccine. Data were not stratified by vaccine brand and included a low representation of Janssen recipients. Moreover, aspects of the implemented case definitions and analytic approach make interpretation of the findings challenging.

Observed-versus expected analysis

The O/E broad and restricted sensitivity analyses on cases in the GMS global safety database reporting POTS or dizziness postural, stratified by 2 age groups and sex, and applying a risk window of day 1 to 90 did not show any evidence for an association between POTS and Ad26.COV2.S. The O/E ratio was <1 in all groups in both the EU and the US. Of note, the background incidence rates used in the O/E analyses were derived from a healthcare database study that used a set of ICD10 codes to define POTS, which may be non-specific and as such overestimate the age-and sex stratified incidence rates (Skufca 2017). This potentially could bias the O/E ratios for POTS towards the null. The O/E results therefore need to be interpreted with caution.

MAH Conclusion: Altogether, based on all available data, including review of individual case reports with POTS or dizziness postural, there is insufficient information to support an association between the event and Ad26.COV2.S vaccine, with no solid conclusion on any causal relationship or underlying mechanisms. Review of cases in the Company global safety database identified 2 cases that met the case definition for POTS, however with confounding comorbidities. Disproportionality results were not consistent across databases and across terms. The individual MedDRA PT Postural orthostatic tachycardia syndrome met the statistical threshold for disproportionality in both the Company global safety database and EudraVigilance, but not in the WHO VigiBase or FDA VAERS databases. O/E analyses did not show any evidence for an association between POTS and Ad26.COV2.S, with the caveat that available background incidence rates possibly were overinflated, potentially biasing O/E ratios for POTS towards the null.

Rapporteur assessment comment:

Overall, results were not consistent across databases and across terms. Only the individual MedDRA PT Postural orthostatic tachycardia syndrome met the statistical threshold for disproportionality in both the GMS global safety database and EudraVigilance, but not in the WHO VigiBase or FDA VAERS databases. No relevant cases fitting to the definition of POTS were detected in the global database. The literature does not indicate a new safety concern with this term.

The O/E broad and restricted sensitivity analyses on cases in the GMS global safety database reporting POTS or dizziness postural, stratified by 2 age groups and sex, and applying a risk window of day 1 to 90 did not show any evidence for an association between POTS and Ad26.COV2.S.

No new safety concern is detected here.

Appetite Disorders

Request: On 15March 2023, Ghana Food and Drugs Authority requested the following:
"*A review of all adverse events described as "appetite disorders" following the administration of COVID-19 Vaccine worldwide to enable the Authority assess and take regulatory action where necessary.*
This is because the Authority has received 35ICSRs of "appetite disorders" from the deployment of the vaccine in Ghana which is not listed in the summary of product characteristics for COVID-19 vaccine Jansen."
MAH Conclusion: Based on this review, there was insufficient evidence to suggest a reasonable possibility that the event may be causally associated with Ad26.COV2.S. vaccine.

Rapporteur assessment comment:

The MAH conclusion regarding appetite disorders can be agreed.

Encephalitis Including Acute Disseminated Encephalomyelitis

On 17 October 2023, a signal of encephalitis including acute disseminated encephalomyelitis (ADEM) with the use of Ad26.COV2.S was identified based on internal review following routine signal detection activities, including individual case review and disproportionality analysis. Previously, a cumulative review of encephalitis including ADEM was conducted (dated 12 October 2021). Based on that review, it was concluded that there was insufficient evidence that encephalitis including ADEM was associated with the use of Ad26.COV2.S. The key factors supporting the conclusion at the time included: reporting rate well within the background incidence rate in the population and limited number of cases with detailed information to associate the causality with the vaccination and rule out alternative etiology, lack of established biological plausibility, and no numerical imbalance from the two large phase 3 double-blinded, placebo-controlled clinical trials.
MAH conclusion: Based on this review, there was insufficient evidence to suggest a reasonable possibility that Ad26.COV2.S is causally associated with encephalitis including ADEM.
Key factors supporting this decision include:

- No clear mechanism of action identified.
- No cases of encephalitis from pooled safety analyses reported in either active/placebo arm.
- A slight increase in O/E ratio was observed in young adults in the US and EU restricted sensitivity analysis. No increase was observed among adults ≥60. This was not replicated in the Real-World Evidence analysis, which showed a lack of evidence of an increased risk in the 1 to 42 days window.
- Within the Company global safety database data, of the 18 cases assessed as BC Levels 1 to 3, only 4 well documented cases were in close temporal association with no confounders. However, 80 cases were not assessable due to limited clinical details (BCC Level 4 and 5). Additionally, 11 (10 primary dose, 1 booster dose) cases occurred outside of the risk window (1 to 42 days).

Rapporteur assessment comment:

Encephalitis including acute disseminated encephalomyelitis (ADEM) was evaluated in depth in 2021 when the use of JCovden vaccine was substantially higher in both EU and US compared to the reporting period of this PSUSA. Based on this review a reasonable possible association could not be supported. In section 2.4 of this PSUSA the data of this item is further presented, which does not suggest need for any further actions.

2.2.1.2. Closed Signals That are Categorised as Important Identified Risks

Myocarditis and Pericarditis

Request:

This topic has been reviewed by the Company in the past. New information has been received that warrants a new review of this topic. On 14 February 2023 a signal was identified for Cardiac inflammatory disease (including myocarditis and pericarditis) with the use of COVID-19 vaccine Ad26.COV2.S based on a request from the US Food and Drug Administration to perform a review of the topic. A full evaluation was completed during the previous PBRER (DLP: 24 February 2023) and an appended as late breaking information. (JNJ- 78436735 [Ad26.COV2.S] Vaccine PBRER 2023).

This topic is further discussed in Section 2.3 Myocarditis and pericarditis.

Closed Signals That are Categorised as Important Potential Risks

No closed signals were categorised as important potential risks.

Closed Signals That are Identified Risks not Categorised as Important

No closed signals were categorised as identified risks not considered important.

Closed Signals That are Potential Risks not Categorised as Important

No closed signals were categorised as potential risks not considered important.

2.2.2. Regulatory Authority Requested Topic

The topic of cutaneous vasculitis was closed in February 2023 and an Ad hoc report was submitted with the previous PBRER reporting interval 25 August 2022 and 24 February 2023 (JNJ- 78436735 [Ad26.COV2.S] Vaccine PBRER 2023). This topic was sufficiently addressed in the previous PBRER with DLD 24 February 2023 hence will not be discussed in the current PBRER.

Use with Concomitant Vaccination

One trial to specifically evaluate the co-administration of Ad26.COV.S with influenza vaccines was conducted (Trial VAC31518COV3005). This was a Phase 3, randomised, double-blind, parallel, multicentre trial to evaluate safety, reactogenicity, and immunogenicity of Ad26.COV2.S co administered with a quadrivalent standard-dose in participants 18 years and above (≥18 to ≤64 years) or high-dose seasonal influenza vaccine in participants 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. Overall, the safety and reactogenicity profile of concomitant administration of Ad26.COV2.S and the standard dose or high dose influenza vaccine is considered acceptable. There were no safety concerns identified from this trial during the reporting interval.

The Company global safety database was searched for medically confirmed and medically unconfirmed cases received during this reporting interval and cumulatively:

Primary dose During this reporting interval, a total of 8 (4 medically confirmed and 4 medically unconfirmed) post-marketing sources (including spontaneous and solicited), initial, primary dose cases reporting the use with concomitant vaccination were identified. There were 2 serious and 6 nonserious cases which reported a total of 30 events (4 serious, 26 nonserious). Cumulatively, 122 (37 medically confirmed and 85 medically unconfirmed) post-marketing, primary dose cases reporting the use with concomitant vaccination were identified. There were 55 serious and 67 nonserious cases which reported a total of 618 events (192 serious, 426 nonserious). The most frequently reported coadministered vaccine type (both during the reporting interval as well as cumulatively) was the influenza vaccine (interval n=4;

cumulatively n=74). Of these 8 cases received, the most frequently (≥2) reported countries/territories of origin were the Netherlands (n=3), and France (n=2). The cases concerned 7 females, and 1 male. The age range was from 32 to 74 years.

Table 22: Frequency Distribution of MedDRA PTs in Post-marketing Primary Dose Cases Reporting Concomitant Vaccination With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Reporting Interval[a]		Number of Events Reported Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
administration				
Influenza	0	1	0	5
Libido disorder	0	1	0	1
Ligament sprain	0	1	0	1
Malaise	0	1	0	15
Muscle spasms	0	1	0	2
Neuromyelitis optica spectrum disorder	1	0	1	0
Premature labour	0	1	0	1
Pulmonary embolism	1	0	5	0
Pulmonary hypertension	1	0	1	0
Sinusitis	0	1	0	2
Skin laceration	0	1	0	1
Tinnitus	0	1	0	1
Upper respiratory tract infection	0	1	0	1
Urinary tract infection	0	1	0	1

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

a: The MedDRA PTs have been presented and sorted by decreasing order for the reporting interval (25 February 2023 to 24 February 2024). A single case may report more than 1 MedDRA PT.

b: For the cumulative column, the events were presented in decreasing order based on the event counts of the current reporting interval (25 February 2023 to 24 February 2024).

Booster Dose During this reporting interval, a total of 13 (all medically unconfirmed) post-marketing, initial cases reported as booster were identified. There were 3 serious and 10 nonserious cases which reported a total of 83 events (10 serious, 73 nonserious). All 13 cases were heterologous. Cumulatively, 106 (16 medically confirmed and 90 medically unconfirmed) post-marketing cases reported as booster were identified. There were 33 serious and 73 nonserious cases which reported a total of 645 events (95 serious, 550 nonserious). Of these cases, 70 were heterologous and 36 were homologous. The most frequently reported co-administered vaccine type (both during the reporting interval as well as cumulatively) was the influenza vaccine (interval n=13; cumulatively n=102). Of these 13 post-marketing cases reported as booster, the most frequently reported country/territory of origin (≥6) was Germany (n=10). These cases concerned 6 females, 6 males, and 1 did not report sex. The age range was from 21 to 77 years.

Table 25: Frequency Distribution of MedDRA PTs in Post-marketing Cases Reported as Booster and Reporting Concomitant Vaccination With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Interval Reporting interval[a]		Number of Events Reported Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserions
Injection site pain	0	11	0	53
Headache	0	9	4	43
Fatigue	0	7	2	47
Myalgia	0	6	1	22
Arthralgia	0	4	1	19
Malaise	0	4	1	22
COVID-19 immunisation	0	3	0	16
Dizziness	0	3	1	15
Back pain	0	2	1	7
Chills	0	2	1	16
Pyrexia	0	2	2	22

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

a. The MedDRA PTs with a frequency ≥2 have been presented. The MedDRA PTs are sorted by decreasing order for the current reporting interval (25 February 2023 to 24 February 2024). A single case may report more than 1 MedDRA PT.

b. For the cumulative column, the events were presented in decreasing order based on the event counts of the current reporting interval (25 February 2023 to 24 February 2024).

Literature ICSR cases received during the current reporting interval were reviewed, and no information was identified that would change the information known about Use with concomitant vaccination.

Rapporteur assessment comment:

No new safety concern was detected for this item.

Vaccine Failure, Lack of Efficacy/Effectiveness

Post-marketing Source Cases

Primary Dose

During this reporting interval, a total of 571 (509 medically confirmed and 62 medically unconfirmed) post-marketing, initial, primary-dose cases reporting events of vaccine failure or LOE were identified. There were 516 serious and 55 nonserious cases which reported a total of 595 EOIs (511 serious, 84 nonserious). Cumulatively, 15,641 (13,063 medically confirmed and 2,578 medically unconfirmed) post-marketing, primary-dose cases reporting events of vaccine failure or LOE were identified. There were 13,778 serious and 1,863 nonserious cases which reported a total of 27,391 (24,359 serious and 3,032 nonserious). Of these 571 cases received during the current interval, the most frequently reported countries/territories of origin (≥10) were Portugal (n=432), the US (n=69), Greece (n=20) and Germany (n=17). These cases concerned 407 males, 104 females, and 60 that did not report sex. The age range was from 18 to 89 years when reported. During the reporting interval, the EOIs (≥5) included drug ineffective (n=287), vaccination failure (n=164), COVID-19 (n=68), suspected COVID-19 (n=43), SARS-CoV-2 test positive (n=9) and thrombosis with thrombocytopenia syndrome (n=7). The mean and median TTO were 85 days and 39 days, respectively, and the range was from 0 to 1,064 days. Of the 595 EOIs, outcomes were reported for 298 as follows: resolved (n=179), resolving (n=91), not resolved (n=20), fatal (n=7), and resolved with sequelae (n=1). Of the total 571 cases received during the interval, 165 medically confirmed reported a TTO >14 days and reported PTs consistent with a COVID-19 diagnosis or laboratory finding of positive PCR test confirming COVID-19 positivity. One of the medically confirmed cases with a TTO >14 days reported the PT suspected COVID-19 or a COVID-19 laboratory test PT with no result.

Figure 3: **Post-marketing Primary-dose Cases Reporting Vaccine Failure or Lack of Efficacy/Effectiveness With the Use of Ad26.COV2.S From the Top 10 Countries/Territories by Month (Interval: 25 February 2023 to 24 February 2024).**

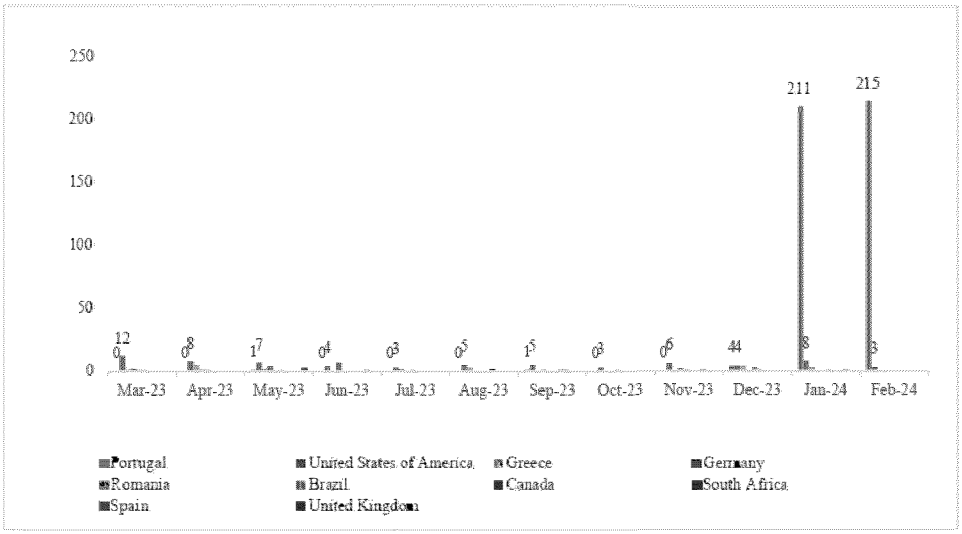
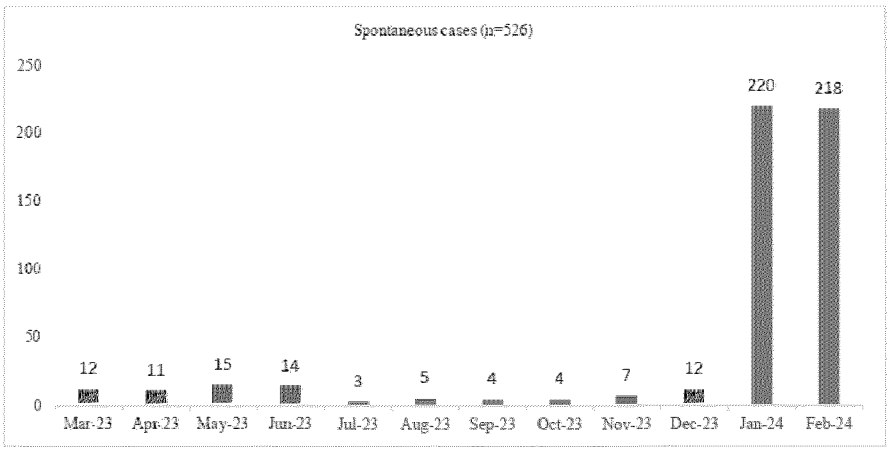


Figure 4: **Case Count of Post-marketing Primary-dose Spontaneous Cases by Month Reporting Vaccine Failure or Lack of Efficacy/Effectiveness With the Use of Ad26.COV2.S (Interval: 25 February 2023 to 24 February 2024).**



Booster Dose

During this reporting interval, a total of 111 (33 medically confirmed and 78 medically unconfirmed) post-marketing, initial cases reported as booster were identified. There were 65 serious and 46 nonserious cases which reported a total of 159 EOIs (75 serious, 84 nonserious). Of these cases, 92 were heterologous and 19 were homologous. Cumulatively, 997 (333 medically confirmed and 664 medically unconfirmed) cases reported as booster were identified. There were 560 serious and 437 nonserious cases which reported a total of 1,435 EOIs (642 serious, 793 nonserious). Of these cases, 631 were heterologous and 366 were homologous. Of these 111 cases reported as booster, the most frequently reported countries/territories of origin (≥7) were the US (n=69), Germany (n=14) and Canada (n=7). These cases concerned 36 females, 36 males, and 39 that did not report sex. The age range was from 24 to 80 years when reported.

The EOIs (≥2) included COVID-19 (n=60), suspected COVID-19 (n=39), vaccination failure (n=33), drug ineffective (n=14), post-acute COVID-19 syndrome, SARS-CoV-2 test positive (n=3 each), COVID-19 pneumonia and breakthrough COVID-19 (n=2 each). The mean and median TTO were 550.2 and 632 days, respectively, and the range was from 0 to 1,133 days. Of the 159 EOIs, outcomes were reported for 74 as follows: not resolved (n=28), resolving (n=24), resolved (n=15), fatal (n=4), and resolved with sequelae (n=3). Of the total 111 cases reported as booster received during interval, 11 medically

confirmed reported a TTO >14 days and reported PTs consistent with a COVID-19 diagnosis or laboratory finding of positive PCR test confirming COVID-19 positivity.

Figure 5: **Post-marketing Cases Reported as Booster and Reporting Vaccine Failure or Lack of Efficacy/Effectiveness With the Use of Ad26.COV2.S From the Top 10 Countries/Territories by Month (Interval: 25 February 2023 to 24 February 2024).**

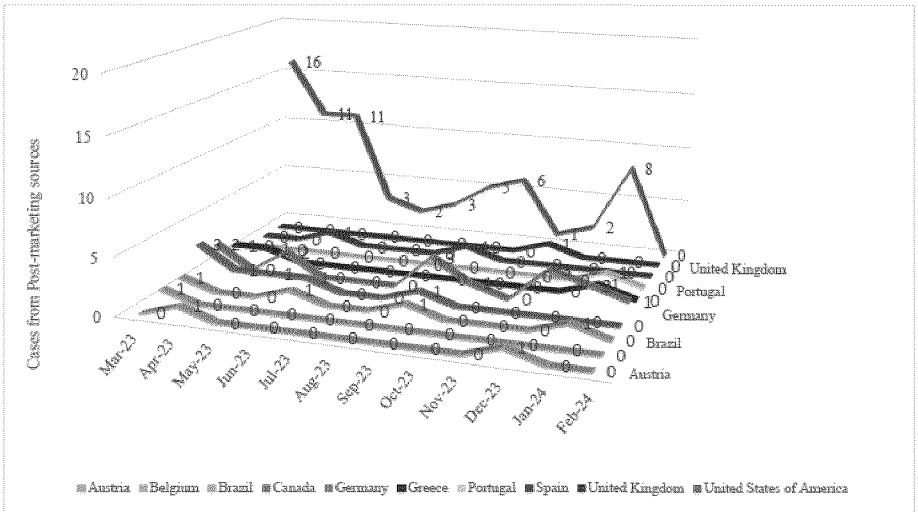
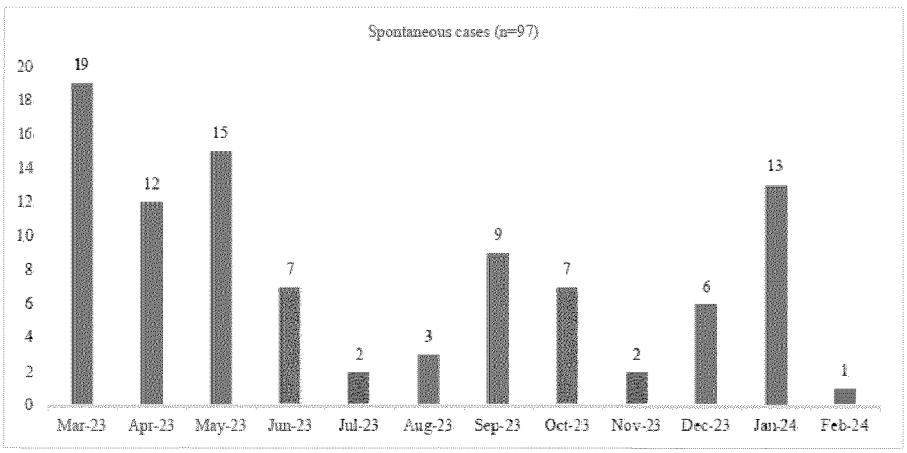


Figure 6: **Case Count of Post-marketing Spontaneous Cases Reported as Booster Reporting Vaccine Failure or Lack of Efficacy/Effectiveness With the Use of Ad26.COV2.S (Interval: 25 February 2023 to 24 February 2024).**



Literature ICSR Fifty-seven ICSR literature cases received during the current reporting interval were reviewed, and no information was identified that would change the information known about vaccine failure or lack of efficacy/effectiveness.

Rapporteur assessment comment:

During the reporting interval, 180 cases of vaccination failure were reported. As described in section "lack of efficacy in clinical trials", reduced VE has been shown for Ad26.COV2.S against the circulating strains of SARS-CoV-2.

Reactogenicity

During the reporting interval, a total of 24 (6 medically confirmed and 18 medically unconfirmed) post-marketing, primary dose cases reporting serious AEs of reactogenicity were identified. These 24 cases reported a total of 52 serious EOIs. Of these 24 cases received, the reported countries/territories of origin were Germany (n=13); the US (n=3); Austria and Spain (n=2 each); and Greece, Korea, Republic

of, Romania, and South Africa (n=1 each). The cases concerned 13 females and 11 males. The age range was from 18 to 71 years. Cumulatively, 1,499 (672 medically confirmed and 827 medically unconfirmed) primary dose cases reporting reactogenicity were identified.

After the primary dose, the reported EOIs were injection site pain (n=3) and injection site erythema, injection site swelling, and vaccination site pain (n=1 each). The mean and median TTO were 1.5 and 2 days, respectively, and the range was from 0 to 3 days. Of the 6 EOIs, outcomes were reported for 3 and are as follows: not resolved, resolved, and resolved with sequelae (n=1 each).

There was no post-marketing, initial booster cases which reported local or systemic reactogenicity reactions. Cumulatively, after primary dose there were 4 medically unconfirmed post-marketing booster cases reported local reactogenicity reactions and after booster dose there were 47 (15 medically confirmed and 32 medically unconfirmed systemic events.

Rapporteur assessment comment:

No new safety concern was detected for this item.

2.3. Evaluation of risks and safety topics under monitoring

New Information on Important Identified Risks

Thrombosis With Thrombocytopenia Syndrome

Results/Discussion

During this reporting interval, a total of 8 (7 medically confirmed and 1 medically unconfirmed) initial, primary dose cases reporting TTS were retrieved. These 8 serious cases reported 28 serious EOI. A single case may report more than 1 EOI. There were no cases retrieved for booster dose from the search of the Company global safety database.

Post-Marketing Sources (Including Spontaneous and Solicited) Cases

Primary Dose

During this reporting interval, a total of 8 (7 medically confirmed and 1 medically unconfirmed) initial, primary dose cases reporting TTS were retrieved. These 8 serious cases reported 28 serious EOIs. Cumulatively, 359 (284 medically confirmed and 75medically unconfirmed) post-marketing, primary dose cases reporting TTS were retrieved. There were 358 serious and 1 nonserious case which reported a total of 1,244 EOIs (1,231 serious, 13 nonserious). A single case may report more than 1 EOI. Of these 8 post-marketing, primary dose cases received (≥2), the most frequently reported countries were the US (n=3) and Germany (n=2). These cases concerned 4 males, 1 female, and 3 cases did not report sex. The age range was from 20 to 54 years.

Table 47: Frequency Distribution 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 Reporting Interval[a]		Number of Events Reported Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
Thrombosis with thrombocytopenia syndrome	7	0	106	0
Pulmonary embolism	3	0	103	0
Acute myocardial infarction	2	0	10	0
Cerebral infarction	2	0	10	0
Deep vein thrombosis	2	0	72	0
Thrombocytopenia	2	0	184	0
Carotid artery thrombosis	1	0	6	0
Cerebrovascular accident	1	0	24	0
Disseminated intravascular coagulation	1	0	20	0
Haemorrhagic stroke	1	0	8	0
Hepatic vein thrombosis	1	0	8	0
Immune thrombocytopenia	1	0	26	0
Ischaemic stroke	1	0	4	0
Platelet count decreased	1	0	102	10
Renal infarct	1	0	7	0
Thrombosis	1	0	77	0

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

a: The MedDRA PTs of interest have been presented for the reporting interval (25 February 2023 to 24 February 2024).

b: For the cumulative column, the event was presented based on the event counts of the current reporting interval (25 February 2023 to 24 February 2024).

The EOIs reported at a frequency ≥2 in these 8 cases were Thrombosis with thrombocytopenia syndrome (n=7), Pulmonary embolism (n=3), Acute myocardial infarction, Cerebral infarction, Deep vein thrombosis, and Thrombocytopenia (n=2 each). The mean and median Time to Onset (TTO) were 213.9 and 13 days, respectively, and the range was from 13 to 716 days. Of the 28 EOIs, outcomes were reported for 13 as follows: not resolved (n=10) and fatal (n=3).

There were no cases retrieved for booster from the search of the Company global safety database.

Clinical Trial Cases

No cases were retrieved from either the Janssen-sponsored clinical or Janssen-supported clinical studies during the reporting interval.

ICSR literature cases received during the current reporting interval were reviewed and no information was identified that would change the information known about TTS.

Line Listings

Death: During the current reporting interval (25February 2023 to 24 February 2024), 1 fatal case was retrieved. This case reported 3 fatal EOIs.

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 information with respect to TTS has occurred during the current reporting interval, which would warrant any update of the product information.

Guillain-Barré syndrome

Results/Discussion

During this reporting interval, a total of 29 (17 medically confirmed and 12 medically unconfirmed) initial, primary dose cases reporting GBS were retrieved. All cases were serious and reported a total of 37 serious EOIs. During this reporting interval, a total of 2 (1 medically confirmed and 1 medically unconfirmed) initial cases reported as booster were identified. Both cases were serious and reported a total of 2 serious EOIs. Both cases were homologous.

Post-marketing Sources (Including Spontaneous and Solicited) Cases

Primary Dose

During this reporting interval, a total of 28 (16 medically confirmed and 12 medically unconfirmed) post-marketing, initial, primary dose cases reporting GBS were retrieved. All cases were serious and reported a total of 36 serious EOIs. Cumulatively, 656 (370 medically confirmed and 286 medically unconfirmed) post-marketing, primary dose cases reporting GBS were retrieved. All cases were serious and reported a total of 702 serious EOIs. Of the 28 post-marketing primary dose cases received, the most frequently reported countries/territories of origin (n≥2) were the US (n=5); Spain (n=4); France, Germany, and Republic of Korea, Republic of (n=3 each); and Portugal (n=2). These cases concerned 14 males, 7 females, and 7 did not report sex. The age range was from 22 to 67 years.

Table 50: Frequency Distribution of MedDRA PTs of Interest in Post-marketing Primary Dose Cases Reporting Guillain-Barré Syndrome With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Reporting Interval[a]		Number of Events Reported Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
Guillain-Barré syndrome	22	0	590	0
Chronic inflammatory demyelinating polyradiculoneuropathy	7	0	56	0
Demyelinating polyneuropathy	3	0	20	0
Miller Fisher syndrome	2	0	21	0
Acute motor axonal neuropathy	1	0	3	0
Bickerstaff's encephalitis	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 interval (25 February 2023 to 24 February 2024). A single case may report more than 1 MedDRA PT.

b: For the cumulative column, the events were presented in decreasing order based on the event counts of the current reporting interval (25 February 2023 to 24 February 2024).

Booster Dose

During this reporting interval, a total of 2 (1 medically confirmed and 1 medically unconfirmed) initial, post-marketing cases reported as booster were identified. Both cases were serious and reported a total of 2 serious EOIs. Both cases were homologous. Cumulatively, 19 (6 medically confirmed and 13 medically unconfirmed) cases reported as booster were identified. All cases were serious and reported a total of 19 serious EOIs. Of these cases, 11 were heterologous and 8 were homologous. Of these 2 post-marketing cases reported as booster, Portugal and US were the reported countries/territories of origin (n=1 each). These cases concerned 1 female and 1 male. The age for 1 case was reported as 69 years and was not reported for other case. The EOI included GBS (n=2). The TTO was not reported in both cases. Of the 2 EOIs, outcomes were reported for 1 and was resolving (n=1).

Janssen-sponsored Clinical Studies

During this reporting interval, no case reporting GBS as primary and booster dose was retrieved.

ICSR literature cases received during the current reporting interval were reviewed, and no information was identified that would change the information known about GBS.

Line Listings

Death: During the current reporting interval (25February 2023 to 24 February 2024), a total of 3 fatal cases were retrieved. However, none of these cases reported a fatal EOI.

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

Results/Discussion

During this reporting interval, a total of 68 (38 medically confirmed and 30 medically unconfirmed) initial, primary dose cases reporting VTE were retrieved. There were 66 serious and 2 nonserious cases, which reported a total of 87 EOI (82 serious and 5 nonserious). During this reporting interval, a total of 16 (13 medically confirmed and 3 medically unconfirmed) initial cases reported as booster cases reporting VTE were retrieved. There were 14 serious and 2 nonserious cases, which reported a total of 18 EOI (16 serious and 2 nonserious). All these cases were homologous cases.

Post-marketing Sources (Including Spontaneous and Solicited) Cases

Primary Dose

During this reporting interval, a total of 61 (31 medically confirmed and 30 medically unconfirmed) post-marketing, initial, primary dose cases reporting VTE were retrieved. There were 60 serious and 1 nonserious case, which reported a total of 79 EOI (76 serious; 3 nonserious). Cumulatively, 2,255(1,535medically confirmed and 720 medically unconfirmed) post-marketing, primary dose cases reporting VTE were retrieved. There were 2,173 serious and 82 nonserious cases, which reported a total of 2,914 EOI (2,801 serious, 113 nonserious). Of these 61 post-marketing, primary dose cases received, the most frequently reported countries/territories of origin (n≥3) were the US (n=38), Germany (n=10), and followed by France (n=3). These cases concerned 32 females, 23 males, and 6 did not report sex. The age range was from 20 to 93 years.

The EOI reported at a frequency ≥5included pulmonary embolism (n=30), deep vein thrombosis (n=24), and pulmonary thrombosis (n=5). The mean and median TTO were 177.2 and 85 days, respectively, and the range was from 0 to 803 days. Of the 79 EOI, outcomes were reported for 34 and are as follows: not resolved (n=13), resolved (n=11), fatal (n=4), resolving and resolved with sequelae (n=3 each).

Booster Dose

During this reporting interval, a total of 15(12 medically confirmed and 3 medically unconfirmed) initial cases reported as booster were retrieved. There were 14 serious and 1 nonserious case, which reported a total of 17 EOI (16 serious; 1 nonserious). All these cases were homologous. Cumulatively, a total of 89 (55medically confirmed and 34 medically unconfirmed) cases reported as booster were identified. Of the 89 cases, 88 were serious and 1 was nonserious. These 89 cases reported a total of 113 EOI (112 serious; 1 nonserious). Of these cases, 62 were homologous and 27 were heterologous. Of these 15post-marketing cases reported as booster, reported countries/territories of origin were the US (n=10); Germany (n=2); followed by Austria, France, and Spain (n=1 each). These cases concerned 10 males and 5females. The age range was from 29 to 81 years. The EOI included pulmonary embolism (n=7); deep vein thrombosis (n=4); thrombophlebitis (n=2); and Budd-Chiari syndrome, central venous catheterisation, pelvic venous thrombosis, and renal vein thrombosis (n=1 each). The mean and median TTO were 259.3 and 268 days, respectively, and the range was from 2 to 518 days. Of the 17 EOI, outcomes were reported for 4 EOI and are as follows: not resolved (n=2) and fatal and resolved (n=1 each).

Epidemiology Data

A retrospective cohort study was conducted to estimate the association between the first dose of JCOVDEN (vs. mRNA) vaccine and VTE among women aged 18 to 49 years across 5 the United States administrative claims databases licensed by the Company between 2021 and 2023. Details of the study are presented in Appendix 7.13.

Clinical Trial Cases

During this reporting interval, a total of 8 clinical cases (7 primary dose and 1 booster) were retrieved from Janssen-sponsored and Janssen-supported Clinical Studies.

Janssen-sponsored Clinical Studies

During this reporting interval, a total of 3 primary dose cases reporting VTE were retrieved from Janssen-sponsored Clinical Studies. Of the 3 cases, 2 were from VAC31518COV3009 and 1 from VAC31518COV3001. These 3 cases concerned male patients and reported 4 EOI (2 serious, 2 nonserious). Of these 3 cases, 2 were reported from the US and 1 was reported from the UK. The age range was from 64 to 75 years. The EOI reported in these cases were pulmonary embolism (n=2) and deep vein thrombosis and superficial vein thrombosis (n=1 each). The mean and median TTO were 563.7 and 700 days, and the range was from 291 to 700 days. The reported outcomes of the EOI are as follows: not resolved (n=2) and resolved and resolving (n=1 each). During this reporting interval, a total of 1 booster case reporting VTE was retrieved from Janssen-sponsored Clinical Studies. This case was reported from VAC31518COV3009 and concerned a 46-year-old female from [redacted] who experienced a nonserious EOI of superficial vein thrombosis. The TTO was 709 days, and the reported outcome was resolved.

Janssen-supported Clinical Studies Cases

During this reporting interval, 4 primary dose cases reporting VTE was retrieved from a Janssen-supported Clinical Study. Three cases were reported from VAC31518COV3021, and 1 case was reported from VAC31518COV3012. These 4 cases reported 4 serious EOI. All cases were reported from South Africa. These cases concerned 3 females and 1 male. The age range was from 37 to 59 years.
The EOI reported in these cases were deep vein thrombosis and pulmonary embolism (n=2 each). The mean and median TTO were 136.5 and 96 days, respectively, and the range was from 7 to 347 days. The outcomes of the EOI are as follows: resolved (n=2) and resolved with sequelae and unknown (n=1 each). During this reporting interval, no cases reported as booster were retrieved from Janssen-supported Clinical Studies.

ICSR literature cases received during the current reporting interval were reviewed, and no information was identified that would change the information known about VTE.

Line Listings

Death: During the current reporting interval (25February 2023 to 24 February 2024), a total of 5 fatal cases were retrieved. Of these cases, 4 cases reported fatal EOI.

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).

A reclassification of VTE from an important potential risk to an important identified risk occurred during the previous reporting interval.

There is no additional new safety concern detected with VTE.

Myocarditis and Pericarditis

Myocarditis and pericarditis were AESIs in the previous PBRER (DLD of 24 February 2023). The cRMP (version 8.0, dated 06 February 2024) and EU-RMP (7.1 version) includes myocarditis and pericarditis as an important identified risk associated with the use of Ad26.COV2.S.

Results/Discussion

During this reporting interval, a total of 21 (12 medically confirmed and 9 medically unconfirmed), primary dose cases reporting myocarditis and pericarditis were retrieved. These 21 serious cases reported a total of 23 serious EOIs. During this reporting interval, a total of 8 (7 medically confirmed and 1

medically unconfirmed) booster cases reporting myocarditis and pericarditis were retrieved. All the 8 cases were serious and reported a total of 10 serious EOIs. All 8 cases were heterologous.

Post-marketing Sources (Including Spontaneous and Solicited) Cases

Primary Dose

During this reporting interval, a total of 20 (11 medically confirmed and 9 medically unconfirmed) post-marketing, initial, primary dose cases reporting myocarditis and pericarditis were retrieved. All these 20 cases were serious and reported a total of 22 serious EOIs. Cumulatively, 458 (263 medically confirmed and 195 medically unconfirmed) post-marketing, primary dose cases reporting myocarditis and pericarditis were retrieved. All the 458 cases were serious and reported a total of 481 serious EOIs. Of these 20 post-marketing, primary dose cases received during the reporting interval, the most frequently reported countries/territories of origin ≥2 were the US (n=6), Germany (n=3), and Netherlands (n=2). These cases concerned 11 males, 6 females, and 3 did not report sex. The age range was from 19 to 74 years. The reported EOIs included myocarditis (n=13), pericarditis (n=7), and myopericarditis (n=2). The mean and median TTO were 171.1 and 32 days, respectively, and the range was from Day 0 to 735days. Of the 22 EOIs, outcomes were reported for 16 and are as follows: not resolved (n=5), resolved (n=4), resolving (n=4), resolved with sequelae (n=2), and fatal (n=1).

Booster Dose

During this reporting interval, a total of 8 (7 medically confirmed and 1 medically unconfirmed) cases reported as booster were identified. All 8 cases were serious. These 8 cases reported a total of 10 serious EOIs. Of these 8 cases, 7 were heterologous and 1 was homologous. Cumulatively, a total of 41 (16 medically confirmed and 25medically unconfirmed) cases reported as booster were identified. All 41 cases reported were serious. These 41 cases reported a total of 46 serious EOIs. Of these 41 cases, 20 were homologous and 21 were heterologous. Of these 8 post-marketing booster cases, reported countries/territories of origin were as follows: Iceland (n=5), Germany, Italy, and South Africa (n=1 each). These cases concerned 6 males, 1 female, and 1 did not report sex. The age range was from 18 to 68 years. The reported EOIs included pericarditis (n=6), myocarditis (n=3), and myopericarditis (n=1). The mean and median TTO were 73.6 and 43 days, respectively, and the range was from 4 to 205days. Of the 10 EOIs, outcomes were reported for 2 and are as follows: not resolved (n=1) and resolved with sequelae (n=1).

Clinical Trial Cases

During this reporting interval, a total of 1 clinical case (primary dose) was retrieved from Janssen-sponsored and Janssen-supported Clinical Studies.

Janssen-sponsored Clinical Studies

During this reporting interval, a total of 1 primary dose case reporting myocarditis was retrieved from Janssen-sponsored Clinical Studies. This case was from VAC31518COV3009 and concerned a 44-year-old male from [redacted] This case reported 1 serious EOI of myocarditis, and the outcome of the EOI was not resolved. During this reporting interval, no case reported as booster was retrieved from Janssen-sponsored Clinical Studies.

Janssen-supported Clinical Studies Cases

During this reporting interval, no case reported as primary dose or booser dose was retrieved from Janssen-supported Clinical Studies.

ICSR literature cases received during the current reporting interval were reviewed, and no information was identified that would change the information known about myocarditis and pericarditis.

Line Listings

Death: During the current reporting interval (25February 2023 to 24 February 2024), a total of 1 fatal case (primary dose) was retrieved. This case reported 1 fatal EOI.

Rapporteur assessment comment

Myocarditis and pericarditis are included in both section 4.4 and 4.8 in the SmPC. This update was done during the reporting interval (II/0072/G). No additional safety information regarding this item was detected here.

Thrombocytopenia (Including Immune Thrombocytopenia)

Table 61: Summary of ASH Case Definition for Thrombocytopenia, including immune thrombocytopenia

	Platelet	Treatment	Antiplatelet 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 antiplatelet 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 antiplatelet 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 Haematology; IVIG=Intravenous Immunoglobulin

Results/Discussion

During this reporting interval, a total of 119 (115 medically confirmed and 4 medically unconfirmed) initial, primary dose cases reporting thrombocytopenia, including immune thrombocytopenia were retrieved. There were 24 serious and 95nonserious cases, which reported a total of 122 EOIs (24 serious, 98 nonserious). During this reporting interval, a total of 25medically confirmed (no medically unconfirmed) initial cases reported as booster were identified. There were 1 serious and 24 nonserious cases which reported a total of 25EOIs (1 serious and 24 nonserious). Of these cases 24 were homologous and 1 did not provide individual patient details.

Post-marketing Source (including spontaneous and solicited) Cases

Primary Dose

During this reporting interval, a total of 20 (16 medically confirmed and 4 medically unconfirmed) post-marketing, primary dose cases reporting thrombocytopenia, including immune thrombocytopenia were retrieved. All cases were serious and included a total of 23 serious EOIs. Out of these 20 cases, 8 cases were assessed as ITP cases per ASH case definition. Cumulatively, 861 (626 medically confirmed and 235 medically unconfirmed) post-marketing, primary dose cases reporting thrombocytopenia, including immune thrombocytopenia were retrieved. There were 742 serious and 119 nonserious cases, which reported a total of 1,010 EOIs (859 serious, 151 nonserious). Out of 861 cases, 429 cases were assessed as ITP cases per ASH case definition. Of these 8 cases received, the reported countries/territories of origin were Germany (n=3); Poland (n=2); and India, Netherlands, and Spain (n=1 each). These cases concerned 6 males and 2 females. The age range was from 21 to 67 years. The EOIs included thrombocytopenia (n=6) and immune thrombocytopenia (n=2). The mean and median TTO were 13.25and 13 days, respectively, and the range was from 13 to 14 days. Of the 8 EOIs, outcomes were reported for 6 and are as follows: not resolved (n=4), resolving (n=1), and resolved (n=1).

Booster Dose

During this reporting interval, 1 serious medically confirmed (no medically unconfirmed) initial case reported as booster was identified. This case pertaining to multiple patients, information regarding individual patients was not reported and also did not qualify as ITP per ASH case definition, hence is not discussed further. Cumulatively, 24 (14 medically confirmed and 10 medically unconfirmed) cases reported as booster were identified. There were 21 serious and 3 nonserious cases which reported a total of 25EOI (16 serious, 9 nonserious). Of these cases, 11 were heterologous and 12 were homologous and in the remaining case pertaining to multiple patients, information regarding individual patients was not reported. Out of 24 cases, 17 cases were assessed as ITP cases per ASH case definition.

Clinical Trial Cases

During this reporting interval, a total of 123 clinical cases (99 primary and 24 booster) were retrieved from Janssen-sponsored Clinical Studies. Of these 123 clinical cases (99 primary and 24 booster), 27 primary dose cases and 14 booster cases were assessed as ITP cases as per ASH criteria. These cases are presented below. No cases were retrieved from Janssen-supported Clinical Studies.

Janssen-sponsored Clinical Studies

During this reporting interval, a total of 27 primary dose cases reporting thrombocytopenia, including immune thrombocytopenia were retrieved from Janssen-sponsored Clinical Studies. Of the 27 cases, 26 were reported from VAC31518COV3009 and 1 was reported from VAC31518COV3001. These 27 cases reported 27 EOIs (26 nonserious and 1 serious). Of these 27 cases, the reported countries/territories of origin were the US (n=8); South Africa (n=5); Colombia, Philippines, and Spain (n=4 each); and Brazil and France (n=1 each). These cases concerned 18 males and 9 females. The age range was from 18 to 82 years. The EOIs included thrombocytopenia (n=22) and platelet count decreased (n=5). The mean and median TTO were 11.04 and 0 days, respectively, and the range was from 0 to 123 days. Of the 27 EOIs, outcomes were reported for 18 and are as follows: resolved (n=15), resolving (n=2), and not resolved (n=1). During this reporting interval, a total of 14 cases reported as booster were retrieved from Janssen-sponsored Clinical Studies. All cases were reported from VAC31518COV3009. These 14 cases reported 14 nonserious EOIs. Of these 14 cases, the countries/territories of origin were the US (n=10), Colombia (n=2), and France and South Africa (n=1). These cases concerned 9 males and 5females. The age range was from 26 to 69 years. The EOIs included thrombocytopenia (n=8) and platelet count decreased (n=6). The mean and median TTO were 95.8 and 95 days, respectively, and the range was from 68 to 122 days. The outcomes were reported as resolved (n=5), resolving (n=2), and not resolved (n=1).

Janssen-supported Clinical Studies Cases

During this reporting interval, there were no cases retrieved from Janssen-supported Clinical Studies.

ICSR literature cases received during the current reporting interval were reviewed, and no information was identified that would change the information known about thrombocytopenia, including immune thrombocytopenia.

Line Listings

Death: During the current reporting interval (25February 2023 to 24 February 2024), a total of 3 fatal cases were retrieved. Of these cases, 1 case reported fatal EOI.

Rapporteur assessment comment:

ITP is listed as AR in the SmPC, section 4.8 and a warning is included in section 4.4. A warning regarding thrombocytopenia is also included in section 4.4. No new safety concern is detected here.

New Information on Important Potential Risks

Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD)

Results/Discussion

Primary Dose

There were no initial, primary dose cases retrieved from the search of the Company global safety database during this reporting interval. Cumulatively, 1 medically confirmed, post-marketing, primary dose case reporting VAED, including VAERD was retrieved. This case reported 1 serious EOI of antibody-dependent enhancement, and the outcome was not reported.

Booster Dose

There were no initial cases reported as booster, which were identified from the search of the Company global safety database during this reporting interval. In addition, cumulatively, there were no cases reported as booster.

Clinical Trial Cases

No cases were retrieved from either the Janssen-Sponsored Clinical or Janssen-Supported Clinical Studies.

No ICSR literature cases were received during the current reporting interval.

Line Listings

Death: During the current reporting interval (25February 2023 to 24 February 2024), no fatal cases were retrieved.

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

New Information on Other Identified or Potential Risks not Categorised as Important

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

2.4. Adverse Events of Special Interest

Cardiac Disorders

Cardiomyopathy

Cardiomyopathy is listed as an AESI in the cRMP, EU-RMP, and the United States Pharmacovigilance Plan (US PVP).

Results/Discussion

During this reporting interval, a total of 4 (3 medically confirmed and 1 medically unconfirmed) initial, primary dose cases reporting cardiomyopathy were retrieved. Of these 4 cases, 3 were serious and 1 was nonserious reporting a total of 4 EOIs (3 serious, 1 nonserious).
During this reporting interval, no case reported as booster was identified.

Post-marketing Sources (Including Spontaneous and Solicited) Cases

Primary Dose

During this reporting interval, a total of 3 (2 medically confirmed and 1 medically unconfirmed) post-marketing, initial, primary dose cases reporting cardiomyopathy were retrieved. Of these 3 cases, 2 were serious and 1 was nonserious reporting 2 serious and 1 nonserious EOIs. These 3 post-marketing, primary dose cases retrieved were reported from the US (n=2) and Belgium (n=1). These cases concerned females, aged 69 and 76 years, and 1 case reported age group as adult.

The EOIs included cardiomyopathy, cardiac hypertrophy, and ischaemic cardiomyopathy (n=1 each). Where reported, the TTO was 2 days and 735 days. The reported outcomes of the EOIs were resolved and not resolved (n=1 each).

Cumulatively, 77 (49 medically confirmed and 28 medically unconfirmed) post-marketing, primary dose cases reporting cardiomyopathy were retrieved. Of these 77 cases, 76 were serious and 1 was nonserious reporting a total of 86 EOIs (82 serious, 4 nonserious).

Booster Dose

During this reporting interval, no post-marketing, initial case reported as booster was identified. Cumulatively, 5(1 medically confirmed and 4 medically unconfirmed) cases reported as booster were identified. All cases were serious and reported a total of 5serious EOIs. Of these cases, 4 were heterologous and 1 was homologous.

Clinical Trial Cases

During this reporting interval, 1 clinical case (primary dose and no booster) was retrieved from Janssen-sponsored clinical trials and no cases were retrieved from Janssen-supported clinical studies.

Janssen-sponsored Clinical Studies

During this reporting interval, 1 primary dose case reporting cardiomyopathy was retrieved from a Janssen-sponsored clinical study (VAC31518COV3009). This case concerned a 65-year-old male from [redacted] who developed a serious EOI of dilated cardiomyopathy 682 days after receiving Ad26.COV2.S vaccine. The outcome of the EOI was reported as not resolved. During this reporting interval, no cases reported as booster were retrieved from Janssen-sponsored clinical studies.

Literature ICSR

No ICSR literature cases were received during the current reporting interval.

Line Listings

Death: During the current reporting interval (25February 2023 to 24 February 2024), no fatal cases were retrieved.

O/E Analysis Results

Table 64: Cardiomyopathy: Restricted O/E and Sensitivity Analysis Results (Cumulative Through 24 February 2024)

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	15.00	3.34	(1.87, 5.51)	6.86	(3.84, 11.32)
	≥60	10.00	0.77	(0.37, 1.41)	2.59	(1.24, 4.76)
EU	18 to 59	7.00	1.36	(0.55, 2.80)	2.79	(1.12, 5.74)
	≥60	5.00	0.49	(0.16, 1.14)	1.65	(0.54, 3.85)

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. Of these, 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 an O/E ratio of >1 for both age groups. Of these, the O/E ratio was statistically significant above 1 (lower bound of 95% confidence interval >1) for the 18 to 59 age group.

MAHs Discussion and Conclusion

Of the 4 primary dose cases received in this interval, majority of the cases concerned females. Ages reported ranged from 65 to 76 years. Two of the cases reported concurrent conditions that confound assessment, and these concurrent conditions included coronary artery disease, hypertension, obesity, and history of smoking (total exposure: 42 packs per year). The TTO ranged from 2 days to 735days. No literature articles were identified during the interval. Overall, no specific patterns among cases reporting cardiomyopathy were identified.

Based on the evaluation of the cases and review of safety from other sources, the information is consistent with previous observations regarding cardiomyopathy following Ad26.COV2.S. No safety concern has been identified; however, based on continued increased O/E results, the Company will continue to monitor cases of cardiomyopathy as an AESI.

Rapporteur assessment comment:

No new safety concern is detected here.

Nervous System Disorders

Encephalitis, Including Acute Disseminated Encephalomyelitis (ADEM) and Meningoencephalitis

Encephalitis, including acute disseminated encephalomyelitis (ADEM) and meningoencephalitis, is listed as an AESI in the cRMP, EU-RMP, and the US PVP. A cumulative review of encephalitis, including ADEM through 24 August 2023

Results/Discussion

During this reporting interval, a total of 6 medically confirmed (no medically unconfirmed) initial, primary dose cases reporting encephalitis, including ADEM and meningoencephalitis, were retrieved. All these 6 cases were serious and reported a total of 9 EOI (all serious). During this reporting interval, no initial cases reported as booster dose were identified.

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

During this reporting interval, a total of 6 (all medically confirmed) post-marketing sources, (including spontaneous and solicited), initial, primary dose cases reporting encephalitis, including ADEM and meningoencephalitis were retrieved. All cases were assessed as serious which reported a total of 9 EOI (all serious).

Cumulatively, 100 (69 medically confirmed and 31 medically unconfirmed) post-marketing, primary dose cases reporting encephalitis, including ADEM and meningoencephalitis were retrieved. All cases were serious and reported a total of 107 serious EOI.

Of these 6 post-marketing, primary dose cases received, the reported countries/territories of origin were the US (n=3), and Portugal, Romania, and South Africa (n=1 each). These cases concerned 2 males, 1 female, and 3 cases did not report sex. The age range was from 33 to 89 years.

The EOI reported at a frequency (≥6) included encephalitis (n=6). The TTO in 1 case was the same day and was not reported for remaining 5cases. Of the 9 EOI, outcomes were reported for 6 and are as follows: not resolved (n=3), resolving (n=2) and resolved (n=1).

Booster Dose

During this reporting interval, no post-marketing, initial cases reported as booster were identified. Cumulatively, 3 (2 medically confirmed and 1 medically unconfirmed) cases reported as booster were identified. All cases were serious and reported a total of 3 serious EOI. Of these cases, 2 were homologous and 1 was heterologous.

Clinical Trial Cases

During this reporting interval, no cases were retrieved from either the Janssen-sponsored clinical or Janssen-supported clinical studies.

Literature ICSR

ICSR literature cases received during the current reporting interval were reviewed, and no information was identified that would change the information known about encephalitis, including ADEM and meningoencephalitis.

Line Listings

Death: During the current reporting interval (25February 2023 to 24 February 2024), 1 fatal case was retrieved. This case did not report fatal EOI.

O/E Analysis Results

Table 67: Encephalitis, ADEM alone: Restricted O/E and Sensitivity Analysis Results (Cumulative Through 24 February 2024)

		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	14.29	0.11	(0.06, 0.19)	1.97	(1.09, 3.29)
		≥60	3.69	0.04	(0.01, 0.11)	0.64	(0.16, 1.71)
	EU	18 to 59	24.00	0.17	(0.11, 0.25)	2.88	(1.85, 4.29)
ADEM	US	18 to 59	7.64	0.61	(0.26, 1.21)	3.16	(1.33, 6.31)
		≥60	0.35	0.2	(0.00, 2.56)	1.02	(0.00, 12.79)
	EU	18 to 59	8.00	0.55	(0.24, 1.09)	2.88	(1.24, 5.67)

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; W/O=Without

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 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). Full US and EU O/E analysis broad and restricted results (to include cumulative exposure, expected counts, background incidence rates) are provided in Appendix 6.2.

ADEM

The US restricted sensitivity analysis showed an O/E ratio of >1 for both age groups. The lower bound of the confidence interval for the male ≥60 age group was <1 in the previous interval. Of these, the O/E ratio was statistically significant above 1 (lower bound of 95% confidence interval >1) for the 18 to 59 age group. The EU 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 lower bound of the confidence interval for the 18 to 59 age group was <1 in the previous interval.

Conclusion

Based on the evaluation of the cases, and review of safety data from other sources, the information retrieved during the reporting interval remains consistent with previous observations regarding encephalitis, including ADEM and meningoencephalitis following Ad26.COV2.S. No safety concern has been identified; however, based on the elevated O/E ratio, and previously confirmed signals for other neuroinflammatory and demyelinating conditions (GBS and TM), the Company will continue to closely monitor cases of encephalitis, including ADEM and meningoencephalitis as an AESI.

Rapporteur assessment comment:

Encephalitis has been repeatedly investigated in earlier PSURs with similar outcomes as presented here. No new safety concern is detected during this PSUR interval.

Multiple Sclerosis (Including Optic Neuritis)

Multiple sclerosis, including optic neuritis, is listed as an AESI in the cRMP, EU-RMP, and the

US PVP.

Results/Discussion

During this reporting interval, a total of 8 (4 medically confirmed and 4 medically unconfirmed) initial, primary dose cases reporting multiple sclerosis, including optic neuritis, were retrieved. All 8 cases were serious and reported a total of 10 serious EOIs. During this reporting interval, a total of 2 medically unconfirmed and no medically confirmed initial cases reported as booster were identified. These 2 cases were serious and reported a total of 2 serious EOIs reporting multiple sclerosis, including optic neuritis. These 2 cases were reported for heterologous booster.

Post-marketing Source (including spontaneous and solicited) Cases

Primary Dose

During this reporting interval, a total of 8 (4 medically confirmed and 4 medically unconfirmed) post-marketing, initial, primary dose cases reporting multiple sclerosis, including optic neuritis, were retrieved. All 8 cases were serious and reported a total of 10 serious EOIs. Cumulatively, 82 (40 medically confirmed and 42 medically unconfirmed) post-marketing, primary dose cases reporting multiple sclerosis, including optic neuritis, were retrieved. All 82 cases were serious and reported a total of 86 serious EOIs.

Of these 8 post-marketing primary dose cases received, the countries/territories of origin were the US (n=3), followed by Czech Republic, Germany, Poland, Slovak Republic, and Zambia (n=1 each). These cases concerned 4 males, 1 female, and 3 that did not report sex. The age range was from 32 to 60 years.

The EOIs included multiple sclerosis (n=5), optic neuritis (n=3), multiple sclerosis relapse, and relapsing multiple sclerosis (n=1 each). The mean and median TTO was 47 days, and the range was from 44 to 50 days. Where reported (n=4), the outcomes were not resolved (n=2), resolved, and resolving (n=1 each).

Booster Dose

During this reporting interval, a total of 2 medically unconfirmed post-marketing, initial cases reported as booster were identified. These 2 cases were serious and reported a total of 2 serious EOIs. These 2 cases were heterologous.

Cumulatively, 10 (4 medically confirmed and 6 medically unconfirmed) post-marketing cases reported as booster were identified. All 10 cases were serious and reported a total of 12 serious EOIs. Of these cases, 7 were heterologous and 3 were homologous.

In these 2 initial post-marketing cases reported as booster, the countries/territories of origin were the US and Italy (n=1 each). Both cases were reported for males. Of these 2 cases, 1 reported the age as 49 years, and the age was not reported in another case. The TTO was reported as 1 day in 1 case and not reported in another. The outcome was reported as not resolved in 1 and was not reported in another case.

Clinical Trial Cases

During this reporting interval, no cases were retrieved from Janssen-sponsored and Janssen-supported clinical studies.

Literature ICSR

ICSR literature cases received during the current reporting interval were reviewed, and no information was identified that would change the information known about multiple sclerosis, including optic neuritis.

Line Listings

Death: During the current reporting interval (25February 2023 to 24 February 2024), 2 fatal cases were retrieved. However, none of these cases reported fatal EOIs.

O/E Analysis Results

Since the previous PBRER DLD (24 February 2023), 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.

Full O/E analysis broad results (to include cumulative exposure, expected counts, background incidence rates) are provided in Appendix 6.2.

MAHs Conclusion

Based on the evaluation of the cases and review of safety data from other sources, the information is consistent with what is currently known about multiple sclerosis, including optic neuritis.

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

Narcolepsy

Narcolepsy is listed as an AESI in the cRMP, EU-RMP, and US PVP. In the second updated PRAC Rapporteur AR (PRAC AR 2023; procedure number EMEA/H/C/PSUSA/00010916/202208) for the Ad26.COV2.S PBRER dated 25February 2022 to

24 August 2022, circulated on 04 April 2023, the rapporteur concluded that the Company should monitor and present the topic in upcoming PBRERs and to "focus on cases that could be true cases of narcolepsy ".

Results/Discussion

During this reporting interval, a total of 25 (4 medically confirmed and 21 medically unconfirmed) initial, primary dose cases reporting narcolepsy were retrieved. There were 14 serious and 11 nonserious cases which reported a total of 25 EOIs (8 serious, 17 nonserious). During this reporting interval, a total of 4 (1 medically confirmed and 3 medically unconfirmed) initial cases reported as booster dose were identified. There were 2 serious and 2 nonserious cases which reported a total of 4 nonserious EOIs. All these 4 cases were heterologous.

Post-marketing Sources (Including Spontaneous and Solicited) Cases

Primary Dose

During this reporting interval, a total of 25 (4 medically confirmed and 21 medically unconfirmed) post-marketing source (including spontaneous and solicited), initial, primary dose cases reporting narcolepsy were retrieved. There were 14 serious and 11 nonserious cases which reported a total of 25 EOIs (8 serious, 17 nonserious).

Cumulatively, 611 (84 medically confirmed and 527 medically unconfirmed) post-marketing, primary dose cases reporting narcolepsy were retrieved. There were 205 serious and 406 nonserious cases which reported a total of 619 EOIs (101 serious, 518 nonserious). Of these 25 post-marketing, primary dose cases received, the most frequently reported countries/territories of origin were Germany (n=16),

followed by the Netherlands (n=3). These cases concerned 15females, 9 males, and 1 case that did not report sex. The age range was from 21 to 71 years.

The EOIs included sleep disorder (n=21), hypersomnia (n=3), and narcolepsy (n=1). The mean and median TTO were 51.1 and 9.5 days, respectively, and the range was from 0 to 242 days. Of the 25 EOIs, outcomes were reported for 21 and are as follows: not resolved (n=13), resolved, resolved with sequelae (n=3 each), and resolving (n=2).

Booster Dose

During this reporting interval, a total of 4 (1 medically confirmed and 3 medically unconfirmed) cases reported as booster dose were identified. There were 2 serious and 2 nonserious cases which reported a total of 4 nonserious EOIs. All these 4 cases were heterologous.

Cumulatively, 53 (6 medically confirmed and 47 medically unconfirmed) cases reported as booster were retrieved. There were 18 serious and 35 nonserious cases which reported a total of 54 EOIs (7 serious; 47 nonserious). Of these cases, 33 were heterologous and 20 were homologous.

All these 4 post-marketing cases reported as booster were reported from Germany (n=4). These cases concerned 2 males and 2 females. The age range was from 29 to 56 years.

Clinical Trial Cases

During this reporting interval, there were no cases were retrieved from either the Janssen- Sponsored Clinical or Janssen-Supported Clinical Studies.

Literature ICSR

ICSR literature case received during the reporting interval was reviewed, and no new information was identified that would change the information known about the AESI narcolepsy.

Line Listings

Death: During the current reporting interval (25February 2023 to 24 February 2024), no fatal cases were retrieved.

Booster: A cumulative CIOMS II LL of cases reported as booster is presented in Appendix 7.24.

O/E Analysis Results

Table 74: Narcolepsy: Restricted O/E Analysis with Sensitivity Analysis Results (Cumulative Through 24 February 2023)

	Restricted O/E Analysis				Sensitivity Analysis	
Region	Age Range (Years)	Observed Counta	O/E Ratio (95% CI)b (PE, 100% RP)		O/E Ratio (95% CI)b (LB, 50% RP)	
EU	18 to 59	113.33	0.89	(0.73, 1.07)	3.41	(2.81, 4.10)
	≥60	23.63	3.24	(2.07, 4.84)	27.38	(17.47, 40.86)

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.

a: Counts included EOI (from valid cases) that occurred within the risk window (Day: 1 to 180) only.

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

The EU 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).

MAHs Conclusion

Based on the evaluation of the cases and review of safety data from other sources, the information retrieved during the reporting interval remains consistent with previous observations regarding

narcolepsy following Ad26.COV2.S. No safety concern has been identified; however, based on previously confirmed signals for other neuroinflammatory and demyelinating conditions (GBS and TM) and the long latency of the disease, the Company will continue to closely monitor narcolepsy as an AESI.

Rapporteur assessment comment:

No new safety concern is detected here.

Vascular Disorders

Cerebrovascular Events

Cerebrovascular events are listed as an AESI in the cRMP, EU-RMP, and US PVP. The Company opened a signal on haemorrhagic cerebrovascular events- based on disproportionate reporting in WHO' s VigiBase. The Company will provide the outcome of this evaluation in the next scheduled PBRER.

Results/Discussion

During this reporting interval, a total of 42 (20 medically confirmed and 22 medically unconfirmed) initial, primary dose cases reporting cerebrovascular events were retrieved. All these serious cases reported a total of 51 EOIs (all serious).

During this reporting interval, a total of 11 (4 medically confirmed and 7 medically unconfirmed) initial cases reported as booster were identified. All these serious cases reported a total of 13 EOIs (all serious). Of these cases, 7 were homologous and 4 were heterologous.

Post-marketing Source (including spontaneous and solicited) Cases

Primary Dose

During this reporting interval, a total of 42 (20 medically confirmed and 22 medically unconfirmed) post-marketing source (including spontaneous and solicited), initial, primary dose cases reporting cerebrovascular events were retrieved. All these serious cases reported a total of 51 EOIs (all serious).

Cumulatively, 1,671 (963 medically confirmed and 708 medically unconfirmed) post-marketing, primary dose cases reporting cerebrovascular events were retrieved. There were 1,669 serious and 2 nonserious cases which reported a total of 2,294 EOIs (2,290 serious; 4 nonserious).

Table 75: Characteristics of Post-marketing Cases Involving the Use of Ad26.COV2.S and Reporting Cerebrovascular Events

Case Characteristics		Nnmher of Cases Received During the Reporting Interval=42	Number of Cases Received Cumulatively=1,671[a]
Sex	Female	20	857
	Male	19	740
	NR	3	74
Age (Years)[b]	18 to 35	6	187
Minimum: 20	36 to 50	6	380
Maximum:88	51 to 64	15	508
Mean: 53.7		8	423
Median: 57	≥65		
	NR	7	159
Sources	Spontaneous	41	1,647
	Clinical study (noninterventional, solicited)	1	24
Country/Territory	United States	18	1,116
	Germany	9	172
	South Africa	6	25
	Italy	2	46
	Romania	2	7
	Colombia	1	6
	Croatia	1	1

Table 75: Characteristics of Post-marketing Cases Involving the Use of Ad26.COV2.S and Reporting Cerebrovascular Events

Case Characteristics		Number of Cases Received During the Reporting Interval=42	Number of Cases Received Cumulatively=1,671[a]
	Malaysia	1	1
	Netherlands	1	45
	Slovenia	1	6
Event Characteristics		**Number of Events=51**	**Number of Events=2,294**
Seriousness (Event Level)[c]	Serious	51	2,290
Outcome (Event Level)[c]	Not resolved	19	867
	Resolving	7	223
	Resolved with sequelae	5	44
	Fatal	1	219
	Resolved	1	280
	Unknown	18	661

Key: EOI=Event(s) of Interest; NR=Not Reported

a: For the cumulative column, the counts were presented in decreasing order based on the current reporting interval (25 February 2023 to 24 February 2024).

b: The median and mean age calculation were based on the current reporting interval (25 February 2023 to 24 February 2024).

c: Seriousness and outcome have been presented for the EOI. A single case may report more than 1 EOI.

Of these 42 post-marketing, primary dose cases received, the most frequently reported countries/territories of origin (n>2) were the US (n=18), followed by Germany (n=9) and South Africa (n=6). These cases concerned 20 females, 19 males, and 3 cases that did not report sex. The age range was from 20 to 88 years.

Table 76: Frequency Distribution of MedDRA PTs of Interest in Post-marketing Primary dose Cases Reporting Cerebrovascular Events With the Use of Ad26.COV2.S

MedDRA PTs	Nnmber of Serious Events Reported During the Reporting Interval[a]	Number of Serious Events Reported Cumulatively[b]
Cerebrovascular accident	22	686
Cerebral infarction	5	111
Transient ischaemic attack	5	142
Carotid artery thrombosis	2	19
Cerebral haemorrhage	2	110
Cerebral ischaemia	2	13
Ischaemic stroke	2	117

Table 76: Frequency Distribution of MedDRA PTs of Interest in Post-marketing Primary dose Cases Reporting Cerebrovascular Events With the Use of Ad26.COV2.S

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 interval (25 February 2023 to 24 February 2024). A single case may report more than 1 MedDRA PT.

b: For the cumulative column, the events were presented in decreasing order based on the event counts of the current reporting interval (25 February 2023 to 24 February 2024).

The EOIs reported at a frequency >2 included cerebrovascular accident (n=22), cerebral infarction (n=5), and transient ischaemic attack (n=5). The mean and median TTO were 59 and 154.5days, respectively, and the range was from 0 to 712 days. Of the 51 EOIs, outcomes were reported for 33 as follows: not resolved (n=19), resolving (n=7), resolved with sequelae (n=5), resolved, and fatal (n=1 each).

Information on Patients ≤40 Years of Age (including fatalities)

During this reporting interval, 1 fatal (primary dose) case was reported in patients ≤40 years of age. In addition, a total of 8 non-fatal (7 primary dose and 1 case reported as booster) cases were reported in patients ≤40 years of age.

One case involved a fatal non-haemorrhagic event (primary dose). A TTO was not reported for that fatal case. The case did not report concomitant medications, diagnostic test results and/or concurrent disease that would confound the case, and reported clean medical history. Of the 8 non-fatal cases, the EOI was outside the 28-day risk window in 4 cases (all primary dose).

Of the remaining 4 cases, assessment in 1case (reported as booster) was confounded by the patients' concurrent disease (obesity). Of the remaining 3 cases (all primary dose cases) 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 interval did not identify evidence suggestive of cerebrovascular events being causally associated with Ad26.COV2.S.

Booster Dose

During this reporting interval, a total of 11 (4 medically confirmed and 7 medically unconfirmed) cases reported as booster were identified. All these serious cases reported a total of 13 events (all serious). Of these cases, 4 were heterologous and 7 were homologous.

Cumulatively, 79 (41 medically confirmed and 38 medically unconfirmed) cases reported as booster were retrieved. There were 78 cases serious and 1 nonserious case which reported a total of 106 EOIs (104 serious; 2 nonserious). Of these cases, 26 were heterologous and 53 were homologous.

Among these 11 post-marketing cases reported as booster, the reported country/territory of origin (>1) was US (n=5), followed by Germany (n=3). These cases concerned 8 males, 1 female, and 2 cases that did not report sex. The age range was from 36 to 93 years.

The EOIs at a frequency >1 included cerebrovascular accident (n=6), ischaemic stroke (n=2), and transient ischaemic attack (n=2). The mean and median TTO were 218.6 and 151 days, respectively, and the range was from 13 to 638 days. Of the 13 EOIs, the outcomes were reported for 6 as follows: not resolved (n=3), resolved, fatal, and resolving (n=1 each).

Clinical Trial Cases

No primary or booster cases were retrieved from either the Janssen-sponsored or Janssen-supported clinical studies.

Literature ICSR

ICSR literature cases received during the current reporting interval were reviewed, and no information was identified that would change the information known about cerebrovascular events.

Line Listings

Death: During the current reporting interval (25February 2023 to 24 February 2024), a total of 5fatal cases were retrieved. These 5 cases, reported 5 fatal cerebrovascular events.

O/E Analysis Results

Table 79: Cerebrovascular Events - Haemorrhagic: Restricted O/E and Sensitivity Analysis Results (Cumulative Through 24 February 2024)

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	9.45	0.35	(0.16, 0.66)	3.08	(1.44, 5.77)
		30 to 39	13.66	0.38	(0.20, 0.63)	4.87	(2.64, 8.22)
		40 to 49	32.73	0.69	(0.48, 0.98)	11.22	(7.71, 15.77)
		50 to 64	62.48	0.44	(0.33, 0.56)	7.15	(5.49, 9.16)
		65 to 74	35.24	0.3	(0.21, 0.42)	3.32	(2.32, 4.62)
		≥75	32.34	0.2	(0.14, 0.29)	2.54	(1.74, 3.58)
	Male	18 to 29	1.70	0.04	(0.00, 0.14)	0.28	(0.03, 1.12)
		30 to 39	9.77	0.16	(0.08, 0.31)	2	(0.95, 3.70)
		40 to 49	20.94	0.28	(0.18, 0.43)	4.58	(2.83, 7.01)
		50 to 64	64.03	0.3	(0.23, 0.38)	4.64	(3.57, 5.92)
		65 to 74	53.67	0.35	(0.26, 0.45)	3.15	(2.36, 4.11)
		≥75	24.38	0.18	(0.12, 0.27)	2.44	(1.57, 3.62)
EU	Female	18 to 29	5.27	2.06	(0.69, 4.71)	11.71	(3.95, 26.77)
		30 to 39	2.21	0.6	(0.08, 2.05)	2.52	(0.35, 8.62)
		40 to 49	11.77	1.21	(0.62, 2.13)	3.69	(1.89, 6.48)
		50 to 64	13.81	0.41	(0.22, 0.69)	1.09	(0.59, 1.83)
	Male	18 to 29	5.30	1.79	(0.60, 4.08)	9.34	(3.16, 21.30)
		30 to 39	7.23	0.89	(0.36, 1.81)	2.95	(1.21, 6.01)
		40 to 49	4.65	0.29	(0.09, 0.68)	0.79	(0.24, 1.89)

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 concerned except the 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 and 40 to 49 and male 18 to 29 and 30 to 39 age groups.

Cerebrovascular Events - Non-Haemorrhagic

Table 80: Cerebrovascular Eveuts – Non-Haemorrhagic: Restricted O/E and Sensitivity Analysis Results (Cumulative Through 24 February 2024)

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	10.66	0.28	(0.14, 0.51)	3.74	(1.84, 6.76)
		30 to 39	17.97	0.21	(0.12, 0.33)	4.32	(2.56, 6.83)
		40 to 49	42.06	0.32	(0.23, 0.43)	7.58	(5.46, 10.24)
		50 to 64	73.16	0.16	(0.12, 0.20)	4.59	(3.60, 5.77)
		65 to 74	39.54	0.1	(0.07, 0.13)	1.31	(0.94, 1.79)
		≥75	51.49	0.09	(0.07, 0.12)	1.15	(0.86, 1.51)
	Male	18 to 29	4.58	0.12	(0.04, 0.30)	1.34	(0.41, 3.25)
		30 to 39	13.63	0.12	(0.07, 0.21)	2.01	(1.09, 3.39)
		40 to 49	19.77	0.11	(0.07, 0.17)	1.98	(1.21, 3.07)
		50 to 64	86.67	0.13	(0.11, 0.17)	2.49	(1.99, 3.07)
		65 to 74	58.54	0.12	(0.09, 0.15)	1.31	(0.99, 1.69)
		≥75	26.31	0.06	(0.04, 0.09)	0.9	(0.59, 1.32)
EU	Female	18 to 29	6.27	0.67	(0.25, 1.44)	2.34	(0.88, 5.02)
		30 to 39	7.21	0.43	(0.18, 0.88)	1.21	(0.50, 2.48)
	Male	18 to 29	9.60	0.92	(0.43, 1.71)	3.14	(1.48, 5.84)
		30 to 39	13.46	0.8	(0.43, 1.36)	2.28	(1.23, 3.86)

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 to28) 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 ≥75 age groups. The lower bound of the confidence interval for the male 65 to 74 age group was <1 in the previous interval. 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 and 65 to 74 age groups.

The EU restricted sensitivity analysis showed an O/E ratio of >1 for both 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 both male age groups.

MAHs Conclusion

Based on the evaluation of the cases and review of safety data 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:

The information presented by the MAH is consistent with the information presented in earlier PSURs. 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 (25August 2021 to 24 February 2022) (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 this PBRER or in future PBRERs. However, a separate subsection is found in the appendix of this PSUR for those regions requiring this information.

2.5. Characterisation of risks

Rapporteur assessment comment: The safety concerns remain unchanged.

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. However, due to the change in viral strains of SARS-CoV-2, these data do not reflecting the efficacy of the vaccine against circulating variants.

Currently there are no new data on efficacy.

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.

After the reporting period of this PSUR, on 10 June 2024, the MAH requested to withdraw the marketing authorisation (EU/1/20/1525/001, EU/1/20/1525/002) for JCovden (EMEA/H/C/005737). The marketing authorisation for JCovden was withdrawn on 9th August 2024 (adopted by the European Commission on 26 July 2024). No valid marketing authorisation is therefore available in the EU/EEA at this time.

5. Rapporteur Request for supplementary information

none

6. MAH responses to Request for supplementary information

NA

7. Comments from Member States

MS comment:

Overall we agree with the assessment of the PRAC Rapporteur. However, we have some comments regarding the B/R assessment. Considering,

- The evolution of the epidemiological context,

- The February 2024 ETF's ETF's statement on the use of recently updated COVID-19 vaccines recommending that the most recently updated COVID-19 vaccines should be used to provide optimal protection against circulating strains,

- The April 2024 ETF's recommendation to updating COVID-19 vaccines to target the new JN.1 variant for the 2024/2025 vaccination campaign and that all marketing authorisation holders are expected to update the composition of their authorised vaccines in accordance with this recommendation,

- The Marketing Authorisation withdrawal adopted by EC on 26 July 2024, with an effective withdrawal date of 9th August 2024 (approved after the circulation of the PRAC AR),

We suggest to have a similar approach as for other COVID-19 vaccines and not to conclude on the B/R balance, nor to maintenance of the MA, which will be withdrawn at the time of the final assessment report.

PRAC Rapp response: The report has been updated according to the comments from MS (see track changes).

Global Medical Safety
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USA

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:
25 February 2023 to 24 February 2024

EUROPEAN UNION REFERENCE DATE:
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APPROVER CREDENTIALS

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On behalf of Dr Laurence Oster-Gozet, EU QPPV

Aggregate Report Scientist:
[redacted]

Medical Safety Officer:
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 interval of 25 February 2023 to 24 February 2024. The content and format of this report follows 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, and guidance outlined in EMA's Consideration on Core Requirements for Risk Management Plan of COVID-19 vaccine. 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 supplied 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 vaccine, an adenoviral vector-based Coronavirus Disease-2019 vaccine, or an inactivated whole virion COVID-19 vaccine. The dosing interval for the heterologous booster dose should be the same as the dosing interval authorised for the booster dose of the vaccine administered 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 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 61 countries/territories and import licenses have been granted in 22 countries/territories worldwide (see Section 2, Worldwide Marketing Authorisation Status).

Exposure

Cumulative Exposure in Clinical Trials

Overall, an estimated 82,240 healthy subjects have been enrolled in the Ad26.COV2.S clinical programme, of which approximately 68,705 subjects received Ad26.COV2.S in the Company-sponsored interventional clinical trials. Of these, 667 subjects were exposed to Ad26.COV2.S in the Phase 1 trials, 935 subjects to Ad26.COV2.S in a Phase 1/2a trial, 2, 419 subjects to Ad26.COV2.S in the Phase 2 trials, and 64,684 subjects to Ad26.COV2.S in the Phase 3 trials.

Additionally, 16,142 subjects were exposed to Ad26.COV2.S in the pre approval access programmes, and 729,517 subjects to Ad26.COV2.S in the interventional clinical studies sponsored by other organisations/institutions (see Section 5.1, Cumulative Subject Exposure in Clinical Trials).

Cumulative and Interval Patient Exposure From Marketing Experience

Cumulative

A total of 660,062,450 doses of Ad26.COV2.S vaccine were distributed and 53,288,029 were administered worldwide from launch to 29 February 2024.

A total of 3,341,040 subjects were administered the homologous Ad26.COV2.S vaccine booster dose in South Africa, South Korea, and the United States (US) from launch to 29 February 2024.

Interval

A total of 48,868,800 doses of Ad26.COV2.S vaccine were distributed and 247,007 were administered worldwide from 01 March 2023 to 29 February 2024.

A total of 227,666 subjects were administered the homologous Ad26.COV2.S vaccine booster dose in South Africa, South Korea, and the US from 01 March 2023 to 29 February 2024. (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-CoV-2 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 variants of concern and variants of interest.

As of 21 January 2024, over 13,463,821,163 doses of the COVID-19 vaccine have been administered Increasing experience based on spontaneous/solicited post-marketing reporting of adverse events, have led to the identification of serious adverse events/reactions such as thrombotic thrombocytopenia syndrome, Guillain-Barré syndrome, immune thrombocytopenia, and myocarditis/pericarditis. 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.

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 caused by SARS-CoV-2.S Spike virus in adults ≥18 years of age. This assessment is based on the following considerations:

- A single dose of Ad26.COV2.S has demonstrated long cellular immunity and protective efficacy against emerging variants (assessed most recently at the beginning of the Omicron period).
- The very rare occurrence of the known safety concerns for the vaccine (mainly identified following primary immunisation). Many of these safety concerns (thrombotic and coagulation disorders, Guillain-Barré syndrome and myocarditis/pericarditis) have also been observed following natural SARS-COV2 infection, with a much higher incidence and severity than following vaccination.
- The current usage pattern of Ad26.COV2.S is centred mainly in low and middle-income countries. The vaccine's profile (single-dose, multi-vial, adaptable to existing cold chain infrastructure) allows

for mass primary vaccination against SARS-COV2 even in remote communities currently under vaccinated against SARS-COV2.S (see Section 18.2, Benefit-Risk Analysis Evaluation).

Actions Taken and Proposed for Safety Reasons

On 31 March 2023, Emerging Safety Issue (ESI) of increased risk of myocarditis and pericarditis was identified following Ad26.COV2.S vaccination (particularly in males under the age of 40 years in the first 2 weeks following vaccination). On 14 April 2023, submission of type II variation to update European Union Prescribing Information; and European Union Risk Management Plan to reflect the important identified risk of myocarditis and pericarditis was filed.

Conclusions

During the reporting interval of this PBRER, a Type II variation to update European Union Prescribing Information; and European Union Risk Management Plan of Ad26.COV2.S to reflect the important identified risks of myocarditis and pericarditis was submitted. During the reporting interval, the CCDS was updated thrice to include "myocarditis and pericarditis", "immune thrombocytopenia", and "reactogenicity" in the adverse reaction section of CCDS. Also, "transvere myelitis" was added to the post-marketing section, warning related to an increased risk of myocarditis/pericarditis in males younger than 40 years of age was added, and text for concomitant use with other vaccines was updated in the "interaction" section. The Company will continue to monitor the safety profile of Ad26.COV2.S to further characterise important identified and potential risks and identify emerging risks if warranted.

Ad26.COV2.S continues to have a favourable benefit-risk profile when used as recommended in the currently approved indication(s). The Company will continue to monitor suspected adverse reactions in association with the use of Ad26.COV2.S. Continuous Company safety monitoring will ensure that updated safety information is available (see Section 19, Conclusions and Actions).

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ACRONYMS/ABBREVIATIONS AND DEFINITIONS OF TERMS

Acronyms/Abbreviations

ACO	Addendum to Clinical Overview
Ad26.COV2.S	Adenovirus Type 26.Coronavirus 2.Spike
ADEM	Acute Disseminated Encephalomyelitis and Meningoencephalitis
ADR	Adverse Drug Reaction
AE	Adverse Event
AEFI	Adverse Event Following Immunisation
AER#	Adverse Event Report Number
AESI	Adverse Event Of Special Interest
AIS	Arterial-Sschemic-stroke
AOSD	Adult-onset Still's Disease
aPL	Anti-phospholipid Antibodies
AR	Adverse Reactions
AWHS	Apple Women's Health Study
BC	Brighton Collaboration
BLI	Biolayer Interferometry
BTI	Breakthrough Infections
CBER	Center for Biologics Evaluation and Research
CCDS	Company Core Data Sheet
CCSI	Company Core Safety Information
CDC	Centers for Disease Control and Prevention
CEM	Cohort Event Monitoring
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CIOMS	Council for International Organisation of Medical Sciences
CoAd	Co-administration
COVID-19	Coronavirus Disease-2019
cRMP	Core Risk Management Plan
CSR	Clinical Study Report
DIBD	Development International Birth Date
DLD/DLP	Data-Lock Date (used for the ease of reading/ understanding – synonymous with Data-Lock Point)
DLS	Dynamic Light Scattering
ECDC	European Centre for Disease Prevention and Control
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
EUA	Emergency Use Authorisation
FAERS	Food and Drug Administration (United States) Adverse Event Reporting System
FDA	Food and Drug Administration (United States)
FOIA	Freedom of Information Act
GBS	Guillain-Barré Syndrome
GBS/MFS	Guillain-Barré syndrome/Miller Fisher syndrome
GMI	Geometric Mean Increase
GMT	Geometric Mean Titre
GVP	Good Pharmacovigilance Practices
HCW	Health Care Workers
HIV	Human Immunodeficiency Virus
HLT	High Level Term

HR	Hazard Ratio
IBD	International Birth Date
IC	Information Component
ICH	International Council on Harmonisation
ICSR	Individual Case Safety Report
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IIR	Important Identified Risk
ILD	Interstitial Lung Disease
IM	Intramuscular
IRR	Incidence Rate Ratios
ITP	Immune Thrombocytopenia
KDCA	Korea Disease Control and Prevention Agency
LMIC	Low and Middle-Income Countries
LL	Line Listing
LOE	Lack Of Efficacy/Effectiveness
MAAEs	Medically-Attended Adverse Events
MAH	Marketing Authorisation Holder (Company)
MCL	Mean Cycle Length
MedDRA	Medical Dictionary for Regulatory Activities
MERS-CoV	Middle East Respiratory Syndrome Related Coronavirus
MIS-C	Multisystem Inflammatory Syndrome (in Children)
MOA	Mechanism Of Action
mRNA	Messenger Ribonucleic Acid
N/A	Not Applicable
NEC	Not Elsewhere Classified
NIU	Noninfectious Uveitis
O/E	Observed versus Expected
OR	Odds Ratio
PBRER	Periodic Benefit-Risk Evaluation Report
PF4	Platelet Factor 4
PRAC	Pharmacovigilance Risk Assessment Committee
PRS	Polygenic Risk Score
PT	Preferred Term (MedDRA)
PVP	Pharmacovigilance Plan
RCT	Randomised-controlled Clinical Trials
RMP	Risk Management Plan
RSA	Republic of South Africa
RSI	Reference Safety Information
RWD/RWE	Real World Data and Real World Evidence
SAE	Serious Adverse Event
SARI	Severe Acute Respiratory Infection
SARS-CoV-2	Severe Acute Respiratory Syndrome-Coronavirus-2 Spike
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SOC	System Organ Class (MedDRA)
SOCV	Single Organ Cutaneous Vasculitis
SPR	Surface Plasmon Resonance
SRS	Spontaneous Reporting System
STS	Signal Tracking System
TFUQ	Targeted Follow-up Questionnaires

TM	Transverse Myelitis
TNCC	Test-Negative Control
TTO	Time to Onset
TTS	Thrombotic Thrombocytopenia Syndrome
UK	United Kingdom
US	United States
VAED	Vaccine-associated Enhanced Disease
VAERD	Vaccine-Associated Enhanced Respiratory Disease
VAERS	Vaccine Adverse Event Reporting System
VE	Vaccine Effectiveness
VITT	Vaccine-Induced Immune Thrombotic Thrombocyt
VOC	Variants of Concern
VOI	Variants of Interest
vp	Virus particles
VTE	Venous Thromboembolism
VUM	Variant Under Monitoring
WHO	World Health Organisation
wt	Wild type
WtVNA	Wild-type Virus Neutralisation Assay
ZEBOV	Zaire Ebola virus

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 interval.
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 interval 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.
Negative dechallenge	Continued presence of an adverse event after withdrawal of a product.

Negative rechallenge	Signs and symptoms similar to those observed when the product was previously used do not reappear when the product is reintroduced.
Non-interventional	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 interval, regardless of whether the last patient last visit has occurred.
Post Authorisation Safety Study (PASS)	A project, whether interventional or non-interventional, 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 non-exposed 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.
Positive dechallenge	Partial or complete disappearance of an adverse event after withdrawal of a product.
Positive rechallenge	Reoccurrence of similar signs or symptoms upon reintroduction of a product.
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 interval of 25 February 2023 to 24 February 2024. The content and format of this report follows 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), and guidance outlined in EMA's Consideration on Core Requirements for Risk Management Plan (RMP) of COVID-19 vaccine.[1]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 supplied 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 vaccine, an adenoviral vector-based COVID-19 vaccine, or an inactivated whole virion COVID-19 vaccine. The dosing interval for the heterologous booster dose should be the same as the dosing interval authorised for the booster dose of the vaccine administered 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.

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 approved doses can be found in Section 1, Introduction. Ad26.COV2.S is authorised in 61 countries/territories and import licenses have been granted in

[1] EMA/PRAC/709308/2022 (dated 01 September 2022)

22 countries/territories worldwide (see Table 1 and Table 2). In addition, Ad26.COV2.S obtained an Emergency Use Listing by the World Health Organisation (WHO).

Table 1: List of Countries/Territories Where Ad26.COV2.S is Authorised (n=61)

Austria	France	Lichtenstein	Slovakia
Bahamas	Gambia	Lithuania	Slovenia
Bangladesh	Georgia	Luxembourg	Solomon Island
Belgium	Germany	Malta	South Africa
Belize	Ghana	Mauritius	South Korea
Brazil	Greece	Moldova	Spain
Bulgaria	Guatemala	Nepal	Sweden
Central African Republic	Guyana	Netherlands	Syria
Chile	Haiti	New Zealand	Trinidad and Tobago
Comoros	Hungary	Nicaragua	Uganda
Croatia	Iceland	Norway	United Kingdom (Great Britain)
Cyprus	India	Panama	United Kingdom (Northern Ireland)
Czech Republic	Ireland	Papua New Guinea	Vanuatu
Denmark	Italy	Poland	
Estonia	Laos	Portugal	
Finland	Latvia	Romania	

Key: n=Number of Countries/Territories

Table 2: List of Countries/Territories Where Ad26.COV2.S is Granted Import Licences (n=22)

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

Key: n=Number of Countries/Territories

3. ACTIONS TAKEN IN THE REPORTING INTERVAL FOR SAFETY REASONS

The following significant actions were taken for safety reasons during the interval covered by this report (see Table 3):

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

Date	Country/Territory	Issue	Action Taken
14 April 2023	European Union	Identification of ESI on 31 March 2023: Analysis of available safety data show an increase in the risk for myocarditis and pericarditis following Ad26.COV2.S vaccination (particularly in males under the age of 40 years in the first 2 weeks following vaccination).	Submission of Type II variation on 14 April 2023 to update EUPI and EU-RMP of JCOVDEN to reflect the important identified risk of myocarditis and pericarditis.

Key: DLP=Data Lock Point; ESI=Emerging Safety Issue; EUPI=European Union Prescribing Information; EU-RMP=European Union Risk Management Plan

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 interval is dated 22 November 2023.

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 Interval

CCDS Version and Date	CCDS Section	Description of Change(s)
Version 016 Dated 22 November 2023	Interactions	Updated text for concomitant use with other vaccines
	Adverse Reactions	Added reactogenicity following administration of TRADENAME with seasonal quadrivalent influenza vaccine (SD or HD) was higher than the vaccines administered alone.
Version 015 Dated 10 October 2023	Adverse Reactions	Addition of post-marketing term "immune thrombocytopenia."
Version 014 Dated 05 April 2023	Warnings and Precautions	Addition of warning related to an increased risk of myocarditis and pericarditis in males younger than 40 years of age.
	Adverse Reactions	Addition of terms myocarditis and pericarditis as post-marketing adverse reactions.
		Addition of term "transverse myelitis" to the post-marketing section

Key: CCDS=Company Core Data Sheet; HD=High Dose; SD=Standard Dose

Please see Appendix 1 for the version of the CCDS in effect at the end of the reporting interval.

5. ESTIMATED EXPOSURE AND USE PATTERNS

5.1. Cumulative Subject Exposure in Clinical Trials

Overall, an estimated 82,240 healthy subjects have been enrolled in the Ad26.COV2.S clinical programme, of which approximately 68,705 subjects received Ad26.COV2.S in the Company-sponsored interventional clinical trials (see Table 5). Of these, 667 subjects were exposed to Ad26.COV2.S in the Phase 1 trials,[2] 935 subjects to Ad26.COV2.S in a Phase 1/2a trial,[3] 2,419 subjects to Ad26.COV2.S in the Phase 2 trials,[4] and 64,684 subjects to Ad26.COV2.S in the Phase 3 trials.[5]

Additionally, 16,142 subjects were exposed to Ad26.COV2.S in the pre-approval access programmes,[6] and 729,517 subjects to Ad26.COV2.S in the interventional clinical studies sponsored by other organisations/institutions.[7]

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[2] Trials included VAC31518COV1002, VAC31518COV1003, and VAC18193RSV2008.
[3] Trial included VAC31518COV1001.
[4] Trials included VAC31518COV2001, VAC31518COV2004, VAC31518COV2008, and VAC31518COV3006.
[5] Trials included VAC31518COV3001, VAC31518COV3003, VAC31518COV3005, and VAC31518COV3009.
[6] Programs included VAC31518COV4006 and VAC31518COV4007.
[7] 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 5: Estimated Cumulative Subject Exposure From Clinical Trials

Treatment	Number of Subjects
Ad26.COV2.S	68,705
Comparator	N/A
Placebo	39,413

Note: Number of participants exposed to at least one study vaccine, recorded in the study databases up to cut-off date (24 February 2024).Trials included: VAC31518COV1001, VAC31518COV1002, VAC31518COV1003, VAC31518COV2001, VAC31518COV2004, VAC31518COV2008, VAC31518COV3001, VAC31518COV3003, VAC31518COV3005, VAC31518COV3006, VAC31518COV3009, and VAC18193RSV2008.

A total of 25,878 participants (506 participants from Trial VAC31518COV1001; 150 participants from Trial VAC31518COV2001; 16,047 participants from Trial VAC31518COV3001; 781 participants from Trial VAC31518COV3005; 151 participants from Trial VAC31518COV3006; and 8,243 participants from Trial VAC31518COV3009) that received a regimen with both Ad26.COV2.S and placebo, participants are counted for both, Ad26.COV2.S and placebo.

Key: N/A=Not Applicable

Table 6 and Table 7 show cumulative subject exposure by age and sex, and by race from completed clinical trials, respectively.

Table 6: Cumulative Subject Exposure to Ad26.COV2.S from Completed Clinical Trials by Age and Sex

Age Range (Years)	Number of Subjects			
	Male	Female	Undifferentiated[b]	Total [a]
12-17	183	146	0	**329**
18-40	9,719	7,270	6	**16,995**
41-64	19,667	17,651	2	**37,320**
65-75	5,605	5,036	0	**10,641**
>75	937	752	0	**1,689**
Total	**36,111**	**30,855**	**8**	**66,974**

a: Data from completed clinical trials as of 24 February 2024.
Completed clinical trials included: VAC31518COV1001, VAC31518COV1002, VAC31518COV1003, VAC31518COV2001, VAC31518COV2008, VAC31518COV3001, VAC31518COV3005, VAC31518COV3006, and VAC31518COV3009.

b: The "undifferentiated" column refers to participants whose sex was reported as "undifferentiated" or "intersex" on the Case Report Form.

Table 7: Cumulative Subject Exposure to Ad26.COV2.S from Completed Clinical Trials by Race[a]

Race Group	Number of Subjects
American Indian or Alaska Native	4,407
Asian	4,008
Black or African American	10,445
Native Hawaiian or other Pacific Islander	150
White	43,485
Multiple	2,625
Unknown	729
Not reported	1,125
Missing	0
Total	**66,974**

a: Data from completed trials as of 24 February 2024.
Completed clinical trials included: VAC31518COV1001, VAC31518COV1002, VAC31518COV1003, VAC31518COV2001, VAC31518COV2008, VAC31518COV3001, VAC31518COV3005, VAC31518COV3006, and VAC31518COV3009.

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 2023) for the United States (US), European Centre for Disease Prevention and Control (ECDC 2023) for European Economic Area (EEA) countries/territories, Korea Disease Control and Prevention Agency (KDCA 2023) for South Korea, Ministério da Saúde (Ministério da Saúde 2021) for Brazil, and National Department of Health (NDH 2023) 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 interval (01 March 2023 to 29 February 2024) is provided in Table 8.

Table 8: Subject Exposure to the Ad26.COV2.S Vaccine During the Reporting interval (01 March 2023 to 29 February 2024)

Region/Country/Territory	Number of Distributed Doses[a]	Number of Administered Doses[b,c]
EEA		
Austria	0	151
Belgium	0	3,255
Bulgaria	0	1,399
Croatia	0	974
Cyprus	0	42
Czechia	0	272
Estonia	0	140
France	0	315
Greece	0	485
Hungary	0	472
Iceland	0	4
Ireland	0	97
Italy	0	5
Latvia	0	79
Lithuania	0	21
Luxembourg	0	22
Norway	0	36
Poland	0	23,041
Portugal	0	2,367
Romania	0	725
Slovakia	0	88
Spain	0	552
ROW		
Afghanistan	3,235,200	NR
Burkina Faso	2,832,000	NR
Burundi	151,200	NR
Cameroon	1,209,600	NR
Central African Republic	1,468,800	NR
Chad	1,101,600	NR
Congo, (Brazzaville)	2,995,200	NR

Table 8: Subject Exposure to the Ad26.COV2.S Vaccine During the Reporting interval (01 March 2023 to 29 February 2024)

Region/Country/Territory	Number of Distributed Doses[a]	Number of Administered Doses[b,c]
Côte D'ivoire	2,371,200	NR
Equatorial Guinea	400,800	NR
Ethiopia	1,634,400	NR
Ghana	1,821,600	NR
Guinea	794,400	NR
Guinea-Bissau	40,800	NR
Haiti	463,200	NR
Kenya	2,076,000	NR
Lesotho	81,600	NR
Liberia	60,000	NR
Madagascar	2,419,200	NR
Malawi	1,046,400	NR
Mali	1,999,200	NR
Mauritania	480,000	NR
Niger	2,200,800	NR
Papua New Guinea	302,400	NR
Senegal	811,200	NR
Sierra Leone	403,200	NR
Somalia	2,601,600	NR
South Africa	0	187,249
South Korea	0	561
South Sudan	993,600	NR
Sudan	5,534,400	NR
Syria (Damascus)	91,200	NR
Syria (North-West)	300,000	NR
Tajikistan	451,200	NR
Togo	453,600	NR
Uzbekistan	3,000,000	NR
Yemen	19,200	NR
Zambia	3,024,000	NR
US	***0***	***24,655***
Total	**48,868,800**	**247,007**

Key: CDC=Centers for Disease Control and Prevention; COVID-19=Coronavirus Disease-2019; 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 the CDC for the US, from the ECDC for the EEA countries/territories, from the KDCA for South Korea, and from the NDH for South Africa.

c: As of 09 August 2021, all entities have the ability to update or delete their previously submitted records. The use of this new functionality may result in fluctuations across metrics on the CDC COVID-19 Data Tracker as historical data are updated or deleted. The functionality will also allow for more accurate reporting and improved data quality. All reported numbers may change over time as historical data are reported to the CDC. In addition, the information within the ECDC website stated that, "*All data are subject to retrospective correction*" which may be a reason for decrease in the cumulative exposure in certain countries/territories. Exposure values were obtained from the most current counts as of 29 February 2024.

A total of 48,868,800 doses[8] of Ad26.COV2.S vaccine were distributed worldwide from 01 March 2023 to 29 February 2024.

A total of 247,007 doses[8] of Ad26.COV2.S vaccine were administered worldwide from 01 March 2023 to 29 February 2024.

Cumulative Exposure Estimates

The cumulative subject exposure for the Ad26.COV2.S vaccine from launch to 29 February 2024 is provided in Table 9.

Table 9: Cumulative Subject Exposure to the Ad26.COV2.S Vaccine (Launch to 29 February 2024)

Region/Country/Territory	Number of Distributed Doses[a]	Number of Administered Doses[b,c]
EEA		
Austria	1,292,400	368,544
Belgium	629,200	431,825
Bulgaria	1,777,300	531,830
Croatia	1,135,150	205,687
Cyprus	190,500	31,075
Czechia	547,200	414,024
Denmark	1,198,800	45,384
Estonia	110,800	79,490
Finland	68,400	NR
France	3,416,300	1,090,907
Germany	7,818,150	3,753,219
Greece	1,521,600	786,508
Hungary	4,309,200	346,000
Iceland[d]	33,500	54,327
Ireland	281,500	241,743
Italy	2,370,000	1,483,508
Latvia	767,800	294,293
Liechtenstein	NR	264
Lithuania[d]	287,200	295,958
Luxembourg	80,200	41,511
Malta	226,800	32,421
Netherlands	2,464,800	750,752
Norway	403,900	7,435
Poland	15,523,300	3,007,456
Portugal[d]	993,600	1,141,885
Romania	4,080,300	2,069,528
Slovakia	475,200	186,679
Slovenia	230,400	135,358
Spain	2,659,000	1,982,248
Sweden	55,200	NR
ROW		
Afghanistan	20,832,050	NR
Algeria	6,508,800	NR
Angola	4,696,050	NR
Antigua and Barbuda	38,400	NR

[8] 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 (Launch to 29 February 2024)

Region/Country/Territory	Number of Distributed Doses[a]	Number of Administered Doses[b,c]
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	6,889,250	NR
Burundi	453,600	NR
Cambodia	1,060,100	NR
Cameroon	6,010,250	NR
Canada	168,000	NR
Central African Republic	4,543,500	NR
Chad	11,465,650	NR
Colombia	11,504,800	NR
Congo (Brazzaville)	5,691,800	NR
Congo, (Kinshasa)	22,965,600	NR
Côte D'ivoire	8,145,400	NR
Djibouti	446,400	NR
Egypt	15,513,450	NR
Equatorial Guine	400,800	NR
Ethiopia	43,394,150	NR
Gabon	866,400	NR
Gambia	777,600	NR
Ghana	11,661,600	NR
Grenada	2,400	NR
Guinea	3,388,800	NR
Guinea-Bissau	1,639,200	NR
Guyana	96,000	NR
Haiti	811,200	NR
Jamaica	216,000	NR
Kenya	17,020,250	NR
Lao PDR	1,771,200	NR
Lebanon	336,000	NR
Lesotho	1,553,850	NR
Liberia	3,271,200	NR
Madagascar	7,209,950	NR
Malawi	6,960,350	NR
Mali	5,332,750	NR
Mauritania	2,964,000	NR
Mauritius	439,200	NR
Mexico	1,350,000	NR
Moldova	302,400	NR
Morocco	302,400	NR
Mozambique	8,989,700	NR
Namibia	676,800	NR
Nepal	3,711,500	NR
Nicaragua	993,600	NR
Niger	7,939,200	NR
Nigeria	75,009,250	NR
Papua New Guinea	1,123,200	NR
Philippines	12,725,650	NR
Rwanda	897,600	NR
Saint Lucia	12,000	NR

Table 9: Cumulative Subject Exposure to the Ad26.COV2.S Vaccine (Launch to 29 February 2024)

Region/Country/Territory	Number of Distributed Doses[a]	Number of Administered Doses[b,c]
Saint Vincent and Grenadines	7,200	NR
Sao Tome and Principe	100,800	NR
Senegal	3,001,500	NR
Sierra Leone	4,651,200	NR
Solomon Islands	100,800	NR
Somolia	2,601,600	NR
South Africa	30,999,200	8,132,856
South Korea	3,411,000	1,515,847
South Sudan	6,856,250	NR
Sudan	22,846,700	NR
Swaziland	302,400	NR
Switzerland	200	NR
Syria (Damascus)	91,200	NR
Syria (North-West)	300,000	NR
Syrian Arab Republic (Syria)	3,458,400	NR
Tajikistan	451,200	NR
Tanzania, United Republic of	34,890,150	NR
Togo	3,074,400	NR
Trinidad and Tobago	259,200	NR
Tunisia	1,540,800	NR
Turkey	832,800	NR
Uganda	23,388,000	NR
Ukraine	1,202,400	NR
Uzbekistan	4,003,150	NR
Vanuatu	43,150	NR
Yemen	1,216,800	NR
Zambia	15,391,050	NR
US	***41,225,650[e]***	***19,007,537***
Total	**660,062,450[f]**	**53,288,029**

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 the CDC for the US, from the ECDC for EEA countries/territories, from the KDCA for South Korea, Ministério da Saúde for Brazil, and from the NDH for South Africa. The data for administered doses for Brazil were last updated by the Ministério da Saúde website on 15 November 2021, and for Germany, the data for administered doses were last updated by ECDC on 17 November 2022.

c: The information within the ECDC website stated that, "*All data are subject to retrospective correction*" which may be a reason for decrease in the cumulative exposure for administered doses in certain countries/territories. Exposure values were obtained from the most current counts as of 29 February 2024.

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: No data on vaccine distribution in the US was reported in LYNX Finance after June 2022

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

A total of 660,062,450 doses of Ad26.COV2.S vaccine were distributed worldwide from launch to 29 February 2024.

A total of 53,288,029 doses of Ad26.COV2.S vaccine were administered worldwide from launch to 29 February 2024.

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	227,666	1,748,144
South Korea[a]	0	27,032
US[b]	0	1,565,864
Total	**227,666**	**3,341,040**

Key: KDCA=Korea Disease Control and Prevention Agency; US=United States
a: The data for administered booster doses for South Korea was last updated by KDCA website on 11 December 2022.
b: The counts also include second booster doses administered in the US.

A total of 227,666 subjects were administered the homologous Ad26.COV2.S vaccine booster dose in South Africa from 01 March 2023 to 29 February 2024.[9]

A total of 3,341,040 subjects were administered the homologous Ad26.COV2.S vaccine booster dose in South Africa, South Korea, and the US from launch to 29 February 2024.[9]

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.

[9] The data for administered booster doses for South Korea was last updated by Korea Disease Control and Prevention Agency website on 11 December 2022.

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 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 Sources (PM Tabulations) inclusion criteria was expanded to include adverse reactions (ARs) from special situation cases (eg, pregnancy, off-label use, 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 interval 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 26.1. 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 serious adverse events (SAE) 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])[10] received cumulatively to the DLD of this PBRER. These ARs are derived from noninterventional 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 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 interval to the next. The ARs displayed in the interval tabulations are not additive to the previous cumulative figure(s).

During the reporting interval, 4,970 serious ARs and 6,620 nonserious ARs were received from spontaneous sources, and 112 serious ARs were received from noninterventional post-marketing studies and other solicited sources.[11] For the reporting interval of 25 February 2023 to 24 February 2024, the AR count is notably less than the number of the ARs

[10] 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.

[11] This does not include interventional clinical trials.

identified from the previous PBRER reporting interval of 25 August 2022 to 24 February 2023 (7,626 serious ARs and 14,821 nonserious ARs). This decrease in number may be due to the lower exposure to the vaccine compared to last reporting interval.

From spontaneous sources, noninterventional post-marketing studies, and other solicited sources, the SOCs including the most reported ARs were:

- General Disorders and Administration Site Conditions (3,157)
- Nervous System Disorders (2,066)
- Musculoskeletal and Connective Tissue Disorders (1,171)
- Gastrointestinal Disorders (639)
- Investigations (598)

Cumulatively, 102,388 serious ARs (101,114 spontaneous, 1,274 from noninterventional post-marketing studies and other solicited sources) were received by the Marketing 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 CSR is available at the time of the DLD for this PBRER reporting interval.

During the reporting interval, 6 Company-sponsored interventional clinical trials (VAC31518COV1001, VAC31518COV2008, VAC31518COV3001, VAC31518COV3005, VAC31518COV3006, and VAC31518COV3009) of Ad26.COV2.S were completed. The safety summary from these completed clinical trials is presented below:

Trial VAC31518COV1001

This was a Phase 1/2a, randomised, double-blind, placebo-controlled, first-in-human, multicentre trial in healthy adults aged ≥18 to ≤55 years and in adults 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 at 6, 12, or 24 months after the primary vaccination regimen administered in Cohort 2.

Of the 1,718 participants screened in this trial, a total of 1,076 participants received at least 1 dose of the trial vaccine (Ad26.COV2.S or placebo). A summary of safety data is presented below:

Safety Summary

The results from the safety and reactogenicity analyses of Cohorts 1 and 2 (adults ≥18 to ≤55 years) and Cohort 3 (adults aged ≥65 years) showed that both the 5×10^{10} vp and 1×10^{11} vp dose levels of Ad26.COV2.S administered as a 1-dose, 2-dose, or booster regimen had an acceptable safety and reactogenicity profile with no significant safety issues identified. Overall, the frequency of AEs reported post-dose 2 was generally similar compared to post-dose 1; however, pyrexia was lower in frequency post-dose 2 than post-dose 1. In addition, lower frequencies of solicited systemic AEs and unsolicited AEs were observed post-booster compared to post-dose 1. In general, a lower reactogenicity was observed for the older adults compared to the younger adults.

Death, Serious adverse events, Adverse Events leading to discontinuation, and AESIs

A total of 5 deaths were reported. One participant died in the 5×10^{10} vp, B: PL group (Cohort 2a) due to asphyxia (Grade 4) during the follow-up post-dose 1, which was considered not related to the trial vaccine by the investigator (homicide). One participant died in the 5×10^{10} vp, 5×10^{10} vp, B: PL group (Cohort 2b) due to suicide (Grade 4) during the follow-up post-booster 1, which was considered not related to the trial vaccine by the investigator. In total, 3 fatal SAEs were reported after unblinding in participants who had already completed their planned vaccination regimen at the time of unblinding (cardiac arrest, haemorrhage intracranial, and aortic aneurysm), all of which were reported in Cohort 3 (including participants ≥65 years). None of these 3 fatal events were considered related to the trial vaccine by the investigator.

Before unblinding, SAEs were reported in 16 participants and after unblinding, SAEs were reported in 36 participants. Except for 2 SAEs, none of the reported SAEs were considered related to the trial vaccine by the investigator.

The SAEs of pyrexia (Grade 3) and multiple sclerosis (verbatim: worsening of multiple sclerosis; Grade 2) were considered related to the trial vaccine by the investigator. The SAE of pyrexia (reported on 28 July 2020) met the criteria for a trial pause. However, the trial was resumed after Data Review Committee review that same day, and no formal pause to the vaccinations occurred in the trial. The SAE of multiple sclerosis was considered not related by the sponsor (no additional information was available). The SAE was ongoing (resolving) at the time of this report.

Twenty-one participants discontinued the trial vaccine due to the following AEs: asphyxia (fatal, homicide), hanging (fatal, suicide), 13 cases of COVID-19, pyrexia, hypertension, nephrolithiasis (SAE), asthma, hypertension, and increased blood pressure. All these AEs were considered not related to the trial vaccine by the investigator, except for pyrexia, hypertension, and increased blood pressure.

No AESIs (ie, thrombotic events with concurrent thrombocytopenia) were reported in this trial. Eight participants had suspected AESIs (thrombotic events and/or thrombocytopenia [defined as platelet count below 150,000/μL,]) in this trial. The suspected AESIs included events of deep vein thrombosis, thrombocytopenia, and ischaemic attack. All suspected AESIs were considered resolved by the time of this report, and all were considered not related to the trial vaccine by the investigator. None of these suspected AESI qualified for review by TTS adjudication committee.

Overall, the results from the safety and reactogenicity analyses of Cohorts 1 and 2 (adults ≥18 to ≤55 years) and Cohort 3 (adults aged ≥65 years) showed that both the 5×10^{10} vp and 1×10^{11} vp dose levels of Ad26.COV2.S administered as a 1-dose, 2-dose or booster regimen had an acceptable safety and reactogenicity profile with no significant safety issues identified.

Trial VAC31518COV2008

This was 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 (5×10^{10} vp or 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 (VAC31518COV2008 Cohort 1 - homologous booster) or who previously received primary vaccination with the Pfizer BNT162b2 vaccine (VAC31518COV2008 Cohort 2 - heterologous booster). The significant safety summary from this trial is described below:

Safety Summary

The results from the descriptive safety and reactogenicity analyses showed that booster vaccination with Ad26.COV2.S at the 5×10^{10} vp, 2.5×10^{10} vp, and 1×10^{10} vp dose levels had an acceptable safety and reactogenicity profile, with no safety issues identified. In general, less reactogenicity was observed in the homologous boosting regimen compared to the heterologous boosting regimen. Also, lower reactogenicity was observed for older adults (≥60 years of age) compared with younger adults (≥18 to 59 years of age), which is in line with previous findings with Ad26.COV2.S vaccination.

Deaths, Serious Adverse Events, Discontinuations due to Adverse Events, and AESIs

There were 2 deaths reported in Cohort 1, 1 malignant neoplasm, and 1 cardiac arrest, 301 days and 98 days post-booster, respectively. Both the AEs led to trial discontinuation. Neither of the fatal events were considered related to booster vaccination.

Twenty participants in Cohort 1 and 15 participants in Cohort 2 experienced SAEs not considered related to vaccination.

There were no SAEs considered related to booster vaccination in Cohort 1. In Cohort 2, 1 participant vaccinated at the 2.5×10^{10} vp dose level experienced 5 Grade 3 SAEs which were all considered related to vaccination. The SAEs were asthenia, headache, nausea, fatigue, and myalgia. All the SAEs had resolved by Day 10 post-booster vaccination.

The AESIs qualified for assessment if thromboembolic events were reported within 42 days of a report of thrombocytopenia/low platelet counts in the same participant. There were no AESIs that qualified for TTS assessment during the trial. Seven AEs of thrombocytopenias were reported in 6 participants, with onset within 19 days after homologous booster vaccination. Of these 7 AEs of thrombocytopenia, 5 were Grade 1 severity and 2 were Grade 3. Both Grade 3 thrombocytopenia AEs were considered related to trial vaccination. All AEs of thrombocytopenia resolved within 15 days of detection, except for 1 case which was reported as resolved 34 days after onset.

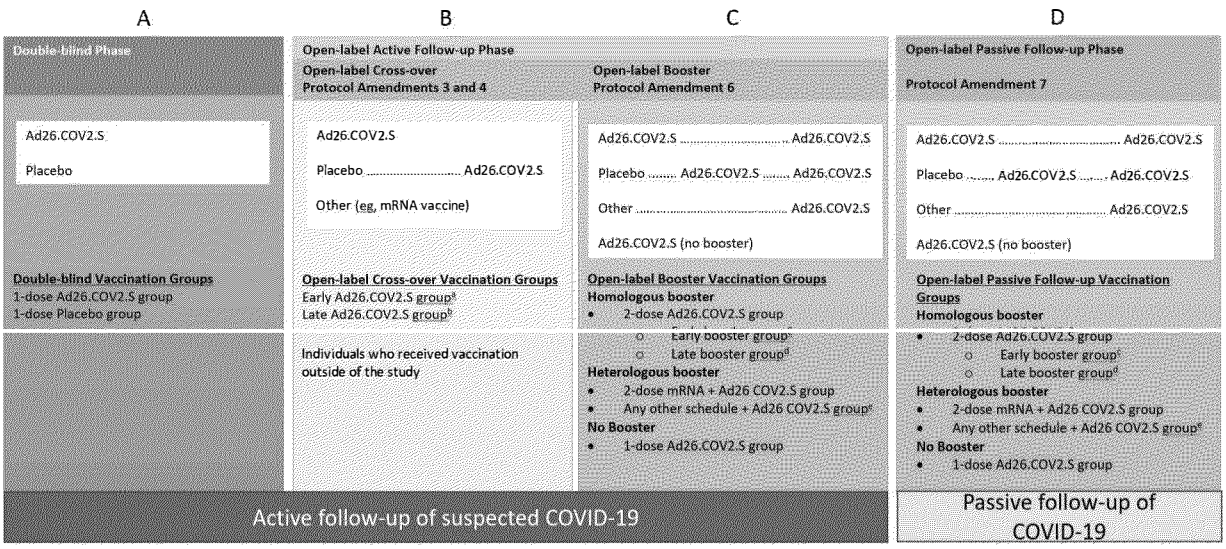
Trial VAC31518COV3001

This was 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 was evaluated in participants living in, or going to, locations with high risk for acquisition of SARS-CoV-2 infection after administration of trial vaccine. All participants who initially received placebo in the double-blind phase were offered a single dose of Ad26.COV2.S at the Month 6/Unblinding Visit. Additionally, the open-label phase of the trial was extended to include an open-label booster vaccination with a single dose of Ad26.COV2.S at the Year 1/Booster Visit. With Protocol Amendment 7, active follow-up of suspected COVID-19 episodes was replaced by passive follow-up (open-label passive follow-up phase). Passive follow-up consisted of safety follow-up phone call visits by the site instead of on-site visits to document safety of the vaccine (such as SAEs or AESIs) and COVID-19 events as (S)AEs and Medically-Attended Adverse Events (MAAEs).

A total of 49,498 participants were screened, of whom 43,788 were randomised and vaccinated with the trial vaccine at Day 1 in a 1:1 ratio (21,898 vaccinated with Ad26.COV2.S and 21,890 received placebo). A summary of safety data is presented below:

- The open-label active follow-up phase (active follow-up of suspected COVID-19 cases) consisting of:
  - The active open-label Ad26.COV2.S cross-over vaccination phase of the placebo group (starting from the unblinding date until the booster visit, See Trial Overview, Panel B, below), and
  - The active open-label Ad26.COV2.S booster vaccination phase (starting from the booster visit until site approval of Protocol Amendment 7, See Trial Overview, Panel C, below).
- The open-label passive follow-up phase (passive follow-up of suspected COVID-19 cases instead of the active follow-up of suspected COVID-19 in the former phases of the trial, as of site approval of Protocol Amendment 7, See Figure 1, Trial Overview, Panel D,).

Figure 1: Trial Overview



[a] Early Ad26.COV2.S group: Participants who received the Ad26.COV2.S vaccine during the double-blind phase.
[b] Late Ad26.COV2.S group: Placebo participants who received the Ad26.COV2.S vaccine as cross-over vaccination.
[c] Early booster group: <6 months (defined by 154 days) between the 2 doses of Ad26.COV2.S.
[d] Late booster group: ≥6 months (defined by 154 days) between the 2 doses of Ad26.COV2.S.
[e] Any other schedule + Ad26 COV2.S group: Participants who received another COVID-19 vaccination schedule outside of the study (eg, non-mRNA [any schedule], only 1 dose of mRNA or more than 2 doses of mRNA) followed by an Ad26.COV.2 booster. This group is only applicable to the safety analysis.

Safety Summary

Deaths, Serious Adverse Events, Discontinuations due to Adverse Events, and AESIs

For the entire double-blind and open-label active phase, the incidence of fatal AEs was 0.42 per 100 PY FU in the Ad26.COV2.S group (186 cases) and 0.77 per 100 PY FU in the placebo group (65 cases), all of which were considered not related to the study vaccine (Ad26.COV2.S or placebo) by the investigator. All deaths reported after Ad26.COV2.S booster vaccination belonged to the late booster group with an incidence of 0.40 per 100 PY FU (55 cases). No deaths were reported in the early booster group (likely due to the small sample size).

For the entire open-label passive phase, the incidence of fatal AEs was 0.51 per 100 PY FU (35 cases) in the Ad26.COV2.S group. No deaths were reported in the placebo group, due to the very low sample size compared to the Ad26.COV2.S group. Most deaths that were reported after Ad26.COV2.S booster vaccination belonged to the late booster group.

During the entire double-blind and open-label active phase, one or more SAEs were reported in the Ad26.COV2.S group with an incidence of 3.55 per 100 PY FU compared with the placebo group (4.92 per 100 PY FU). Most of the SAEs belonged to the SOC of infections and infestations (PTs: COVID-19 and COVID-19 pneumonia).

During the entire open-label passive phase, 1 or more SAEs were reported in the Ad26.COV2.S group with an incidence of 2.61 per 100 PY FU compared with the placebo group (9.23 per 100 PY FU). Most SAEs were not associated with COVID-19 and reported in the Ad26.COV2.S group with an incidence of 2.58 per 100 PY FU compared with the placebo group (9.23 per 100 PY FU).

Only 1 SAE of a thromboembolic event with thrombocytopenia (PTs: Venous transverse sinus thrombosis and Cerebral haemorrhage) was classified as TTS meeting both Level 1 criteria using the BC level of certainty and the Centers for Disease Control and Prevention definition for a Tier 1 TTS case. The case met the PRAC criteria of a Confirmed case of TTS.

Fewer AEs were reported in the homologous Ad26.COV2.S booster group compared to the heterologous booster groups (Ad26.COV2.S booster after 2 doses of mRNA group and Ad26.COV2.S booster after any other schedule group). Overall, a higher reactogenicity profile was observed for the heterologous booster groups compared with the homologous Ad26.COV2.S booster group. During the open-label passive phase, the number of AEs/SAEs reported was reduced compared to the combined double-blind and open-label active phase, as this might be expected due to the nature of the follow-up. No difference was observed in the safety profile of the Ad26.COV2.S booster when received within 6 months (early booster) or more than 6 months (late booster) after the first Ad26.COV2.S dose. Beyond the single TTS case reported during the double-blind phase of the study, no new cases of TTS were identified. There were less AEs observed post-dose 2 of Ad26.COV2.S compared to post-dose 1 of Ad26.COV2.S. In the combined double-blind and open-label active phase, there were more fatal AEs reported compared with the open-label passive phase. Most fatal AEs were reported in the Ad26.COV2.S group of which all were considered not related to the study vaccine. Related SAEs either associated or not associated with COVID-19 were reported less in the open-label passive phase compared to the combined double-blind and open-label active phase. No conclusions can be drawn for the mixed schedule group. No new safety concerns were identified.

During the entire trial, 4 AEs leading to termination of study participation were reported in 3 participants after receiving at least 1 dose of Ad26.COV2.S. All events were reported in the late booster group (Grade 3 myocardial infarction and Grade 3 pneumonia in 1 participant, Grade 3 glioblastoma in 1 participant, and Grade 1 alopecia in the other participant). In the placebo group, 5 events were reported in 2 participants (1 participant reported an AE of Grade 3 ophthalmic herpes zoster and another participant reported AEs of Grade 3 acute kidney injury, Grade 4 COVID-19, and 2 events of Grade 4 fall). None of the events were considered related to the study vaccine by the investigator. No AEs leading to study discontinuation were reported in participants that received Ad26.COV2.S as a heterologous booster.

Trial VAC31518COV3005

This was a Phase 3, randomised, double-blind, parallel, multicentre trial to evaluate the safety, reactogenicity, and immunogenicity of Ad26.COV2.S co-administered with a quadrivalent standard-dose in participants 18 years and above (≥18 to ≤64 years) or high dose seasonal influenza vaccine in participants 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. A summary of the safety findings from this trial is presented below:

Safety analyses showed slightly higher reactogenicity after concomitant administration of Ad26.COV2.S and influenza vaccine (standard-dose or high dose) than after separate administration of each vaccine, but the safety and reactogenicity profile of Ad26.COV2.S

administered concomitantly with the influenza vaccine is in line with the profile of Ad26.COV2.S observed in previous trials.

Safety Summary

Deaths, Serious Adverse Events, Discontinuations due to Adverse Events, AESIs

An AE with fatal outcome (Grade 4 cardiac arrest) was reported in 1 (2.1%) participant in Group 3 after concomitant administration of the Ad26.COV2.S and influenza vaccine (high dose). This participant had the following active medical conditions at study entry: atrial fibrillation, hypertension, type 2 diabetes mellitus, and gastroesophageal reflux disease. The event was considered by the investigator as not related to the study vaccines.

Serious adverse events were reported in 2.4% (9/382) of participants in Group 1, 1.8% (7/384) of participants in Group 2, 2.1% (1/47) of participants in Group 3, and 4.3% (2/46) of participants in Group 4. Most SAEs were Grade 3 in severity. Two SAEs were Grade 4 in severity (cardiac arrest and pulmonary embolism). None of the SAEs were considered related to study vaccine by the investigator, except for the event of deep vein thrombosis in 1 participant in Group 1 and the events of thrombocytopenia in 1 participant in Group 1 and 1 participant in Group 2.

Adverse events leading to permanent discontinuation of vaccination were reported in 1 (0.3%) participant in Group 1 after concomitant administration of Ad26.COV2.S and influenza vaccine (standard dose) (Grade 2 urticaria considered related to study vaccine) and in 1 (2.1%) participant in Group 3 after concomitant administration of Ad26.COV2.S and influenza vaccine (high dose) (Grade 4 cardiac arrest).

In the standard-dose groups, the following suspected AESIs were reported: deep vein thrombosis (in 1 participant in Group 1), heparin-induced thrombocytopenia[12] (in 1 participant in Group 1), pulmonary embolism (in 1 participant in Group 2), thrombocytopenia (in 5 participants in Group 1 and 9 participants in Group 2) and platelet count decreased (in 2 participants in Group 1 and 3 participants in Group 2). None of the participants had thrombosis and thrombocytopenia concomitantly; therefore, none of the suspected AESIs qualified for TTS assessment.

Concomitant administration of the vaccines did not impact the durability of the influenza- and SARS-CoV-2-specific humoral immune responses as there were no relevant differences between the Co-Administration CoAd and control groups during the 6-month follow-up period. This was also reflected in similar seroprotection and seroconversion rates between the groups and across the 4 influenza vaccine strains.

[12] The verbatim term as reported by the investigator was "positive HIT(t) ELISA test", which was coded into the MedDRA preferred term "heparin induced thrombocytopenia". The heparin induced thrombocytopenia antibody test was positive, but without clinical significance (no signs and symptoms). There was no low platelet count at any point in time.

Overall, the safety and reactogenicity profile of concomitant administration of Ad26.COV2.S and the standard-dose or high-dose influenza vaccine is considered acceptable. No safety concerns were identified.

Trial VAC31518COV3006

This was a Phase 2, randomised, observer-blind trial to evaluate the safety, reactogenicity, and immunogenicity of different dose levels of Ad26.COV2.S administered as a 1- or 2-dose regimen in healthy adolescents aged 12 to 17 years inclusive. A summary of safety findings from this trial is presented below:

Safety Summary

Deaths, Serious Adverse Events, Discontinuations due to Adverse Events, AESIs

One death by intentional overdose (intentional calcium channel blocker overdose) was reported in the 1.25×10^{10} vp dose group in the 1 dose primary regimen during the booster follow-up 1 period. This fatal AE was considered not to be related to the study vaccine by the investigator.

Following SAEs were reported in 3 participants: Grade 3 femur fracture, Grade 3 vaginal cyst excision, and 1 fatal SAE of Grade 4 intentional overdose (intentional calcium channel blocker overdose). These SAEs were not considered related to study vaccine by the investigator.

No AEs leading to study vaccine discontinuation were reported in any dose group.

Thrombosis with TTS and Multisystem Inflammatory Syndrome (in Children) (MIS-C) were considered AESIs in this trial. One participant experienced an event of platelet count decreased 1 day after the first vaccination, that was evaluated as a case of suspected AESI. The suspected AESI did not qualify for TTS assessment as the participant did not have thrombosis and thrombocytopenia concomitantly, thus, no case of TTS was detected in this trial. Also, no cases of MIS-C were reported during the trial.

Overall, the safety and reactogenicity profile of the Ad26.COV2.S at the 2.5×10^{10} vp (per 0.25 mL and 0.5 mL), 1.25×10^{10} vp, and 0.625×10^{10} vp dose levels is considered acceptable. No unexpected safety concerns were identified.

Trial VAC31518COV3009

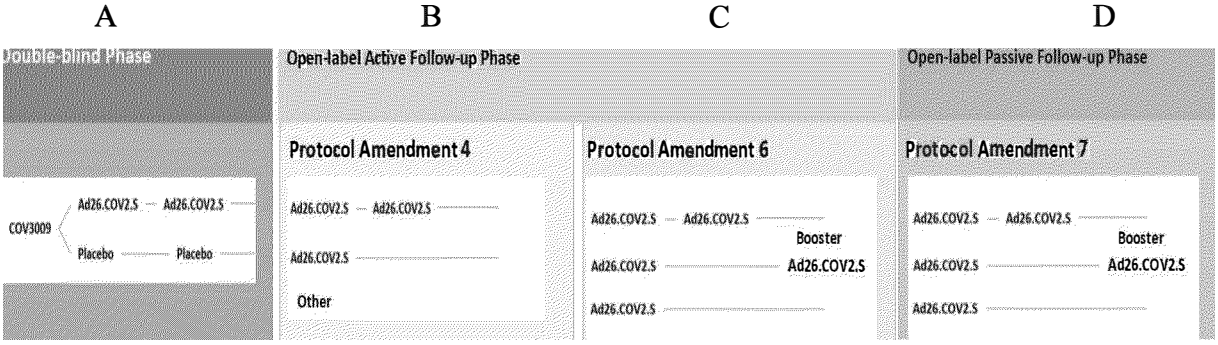
This was a Phase 3, randomised, double-blind, placebo-controlled, multicentre, pivotal efficacy and safety trial in adults ≥18 years of age. The efficacy, safety, and immunogenicity of Ad26.COV2.S was evaluated in participants living in, or going to, locations with high risk for acquisition of SARS-CoV-2 infection after administration of 2 doses of study vaccine. All eligible participants who initially received placebo in the double-blind phase were offered a single dose of Ad26.COV2.S (open-label vaccination) and subsequently, eligible participants

who only received a single Ad26.COV2.S vaccination were offered an open-label booster vaccination. All booster vaccinations have now been completed.

The following phases are included as presented in the Study Overview below:

- The double-blind phase (starting from the date of first study vaccination until the unblinding date; see Study Overview, Panel A, below).
- The open-label active follow-up phase (active follow-up of suspected COVID-19 cases starting from the unblinding date until site approval of Protocol Amendment 7; see Study Overview, Panels B and C, below).
- The combined double-blind and open-label active phase (starting from the date of first study vaccination until site approval of Protocol Amendment 7; see Study Overview, Panels A, B, and C, below).
- The open-label passive follow-up phase (passive follow-up of suspected COVID-19 cases instead of the active follow-up of suspected COVID-19 in the former phases of the trial, as of site approval of Protocol Amendment 7; see Figure 2 Study Overview, Panel D, below).

Figure 2: Trial Overview



At the end-of-study analysis, a total of 31,705 participants were included in the Full Analysis Set (FAS) of the combined double-blind and open-label active phase. For the open-label passive phase, 24,342 participants were included in the FAS7 (at study start, 13,094 participants received Ad26.COV2.S and 11,248 participants received placebo). For the analysis of safety, data are compared between 24,105 participants who had received at least one dose of Ad26.COV2.S and 15,613 placebo recipients from the combined double-blind and open-label active phase. Additionally, safety data for the open-label passive phase are compared between 11,043 participants who had received at least 1 dose of Ad26.COV2.S during the combined double-blind and open-label active phase and the 360 participants who remained in the placebo group at the time of study site approval of Protocol Amendment 7. A summary of safety data is presented below:

Safety Summary

Deaths, Serious Adverse Events, Discontinuations due to Adverse Events, AESIs

For the entire double-blind and open-label active phase, the incidence rates of 1 or more fatal AEs (including COVID-19 related deaths) were comparable with 0.30 per 100 PY FU in at least 1 dose Ad26.COV2.S group (in 71 participants) and 0.38 per 100 PY FU (in 17 participants) in the placebo group. All events were considered not related to the study vaccine (Ad26.COV2.S or placebo) by the investigator, except for 1 event of respiratory distress (Grade 4) in 1 participant that was considered related. This participant who received placebo during the double-blind phase was reported with a Grade 4 SAE of respiratory distress on the night of receiving the open-label Ad26.COV2.S. This death was considered related to the placebo vaccination during the double-blind phase by the investigator and was considered not related by the Sponsor.

For the entire open-label passive follow-up phase, the incidence of fatal AEs (including COVID-19 related deaths) was 0.30 per 100 PY FU in the at least 1 dose Ad26.COV2.S group (in 21 out of 11,043 participants), which were all considered not related to the study vaccine by the investigator. No fatal events were reported for the placebo group (ie, 360 participants).

During the entire double-blind and open-label active phase, 1 or more SAEs were reported in at least 1 dose Ad26.COV2.S group with an incidence of 3.04 per 100 PY FU compared with the placebo group that had a higher incidence of 4.10 per 100 PY FU. Most of the SAEs belonged to the SOC of infections and infestations (PTs: COVID-19 and COVID-19 pneumonia). During the entire open-label passive follow-up phase, 1 or more SAEs were reported in at least 1 dose Ad26.COV2.S group with an incidence of 1.97 per 100 PY FU compared with the placebo group that had a lower incidence of 1.46 per 100 PY FU. Most of the SAEs of at least 1 dose Ad26.COV2.S group belonged to the SOC of infections and infestations with an incidence of 0.33 per 100 PY FU (PTs: Pneumonia and Sepsis).

No cases of TTS were identified by the AESI Adjudication Committee during the entire trial. Incidence rates of MAAEs per 100 PY FU were lower in at least 1 dose Ad26.COV2.S group (18.49 per 100 PY FU) compared to the placebo group (31.49 per 100 PY FU) during the combined double-blind and open-label active phase.

7.2. Ongoing Clinical Trials

An "ongoing clinical trial" is defined as a trial for which the first ICF has been signed, but for which a final CSR is not available at the DLD for this PBRER reporting interval, regardless of whether the last participant last visit has occurred.

During the reporting interval, 3 Company-sponsored, interventional clinical trials (VAC31518COV2004, VAC31518COV3003, and VAC18193RSV2008) of Ad26.COV2.S were ongoing. These clinical trials are briefly summarised below:

- **Trial VAC31518COV2004:** This is a Phase 2, open-label, multicentre trial to evaluate the safety, reactogenicity, and immunogenicity of Ad26.COV2.S in healthy pregnant (2^{nd} and/or 3^{rd} trimester of pregnancy) participants aged ≥18 to ≤45 years. In this trial,

Ad26.COV2.S will be assessed as a single dose in pregnant women who were previously vaccinated with another COVID-19 vaccine regimen or who were vaccine naïve at study entry

No significant safety findings were identified from this trial during the reporting interval.

- **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 enrolled 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 TTS events.

  No significant safety findings were identified from this trial during the reporting interval.

- **Trial VAC18193RSV2008:** This is a Phase 1, randomised, observer-blind, multicentre trial to evaluate innate and pro-inflammatory responses of an Ad26.RSV.preF-based vaccine, Ad26.COV2.S and Ad26.ZEBOV vaccine in adult participants aged 18 to 59 years in stable health.

  No significant safety findings were identified from this trial during the reporting interval.

Independent Data Monitoring Committee/Data Safety Monitoring Board

During the reporting interval, 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 during the reporting interval.

7.4. Other Therapeutic Use of Medicinal Product

No other programs that follow a specific protocol (solicited reporting as per ICH E2D) were conducted for Ad26.COV2.S during the reporting interval.

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 interval, no new information with potential impact to the benefit-risk assessment has been identified (see Appendix 4.2). Summary from Real World Evidence (RWE) studies is presented below:

Real World Evidence Summary for Ad26.COV2.S

The Company-sponsored (VAC31518COV3021, VAC31518COV4002, VAC31518COV4004, and VAC31518COV4019), collaborative, and publicly available RWE studies/trials reporting on the VE of Ad26.COV2.S are described below. As these studies assessed vaccine effectiveness and not safety, no safety data is reported here:

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 is being 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 DLD of this PBRER, 250,878 participants received Ad26.COV2.S in this study.

In addition, this trial 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). Vaccine efficacy (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.

Study VAC31518COV4002

Final results (up to 12 months after vaccination; median follow-up ranging from 243 days to 268 days) are available from this study, 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 VE results in Janssen's large, longitudinal US cohort study demonstrated effective and stable VE for the single-dose Ad26.COV2.S, based on month-on-month analysis and Kaplan-Meier plots through the end of September 2022. There have been several other RWE studies that have been recently published by researchers, that evaluate the VE of single-dose Ad26.COV2.S. 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 literature, it is confirmed that there was a benefit to 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 in Study VAC31518COV4002 and the booster dose Ad26.COV2.S in Study VAC31518COV3021.

Study VAC31518COV4004

Final results were available for this study, multicentre, multi-country, hospital-based case-control study with test negative case-control design to assess the absolute effectiveness of a single-dose of Ad26.COV2.S in comparison to no vaccine against laboratory-confirmed SARS-CoV-2 SARI hospitalisations as well as estimate effectiveness for different age groups, those identified with certain chronic conditions, immunocompromised individuals, duration since vaccination, and related to specific SARS-CoV-2 variants.

The final results from this study with data collection through February 2023 demonstrated that a single-dose of Ad26.COV2.S provided protection against laboratory confirmed SARS-CoV-2 SARI hospitalisations. This protection persisted for up to 6 months after vaccination. No significant differences were seen when stratified by age, chronic medical condition, time since dose, or period of specific SARS-COV-2 variants. There was lack of precision, particularly for stratified analyses, due to the small number of enrolled vaccine recipients.

Study VAC31518COV4019

Final results (with 12 months of follow-up time from the date of booster vaccination for an exposed individual and the corresponding date for the matched individual in the referent group) were available from this study, an observational, longitudinal cohort study of individuals in the US to assess the relative effectiveness of heterologous and homologous booster vaccination in preventing COVID-19 related hospitalisations in individuals who completed an FDA-authorised or approved COVID-19 primary vaccination series (Ad26.COV2.S [1 dose], BNT162b2 [2 doses], and mRNA-1273 [2 doses]) using both open and closed-claims data elements aggregated by Health Verity.

The final results from this study demonstrated that both homologous and heterologous booster vaccines provided protection against COVID-19 related hospitalisations for up to 12 months. There have been other RWE studies that have been recently published by researchers, that evaluate the VE of single dose and booster Ad26.COV2.S. The protection against COVID-19 varies between different Variants Of Concerns (VOCs). Single dose Ad26.COV2.S VE against infection was reported to be lower during Omicron-emerging and Omicron-predominated periods. Vaccination remained more effective in preventing hospitalisation and death during the Omicron-emerging and Omicron-predominated periods. Vaccine effectiveness against COVID-19 infections and COVID-19-related hospitalisation was observed in fully vaccinated

individuals who received a booster dose. Fully vaccinated individuals who received heterologous Ad26.COV2.S or mRNA booster vaccines showed an increase in VE compared with homologous dose Ad26.COV2.S or mRNA vaccines during the Omicron periods as reported in RWE studies. This literature confirms the benefit of a heterologous Ad26.COV2.S booster dose in protecting against COVID-19 related infections, hospitalisations, and deaths, also during the Omicron period.

9. INFORMATION FROM OTHER CLINICAL TRIALS AND SOURCES

9.1. Other Clinical Trials

9.1.1. Completed Clinical Study

During the PBRER reporting interval, 1 interventional clinical study (VAC31518COV3012 [Sisonke {Together}]) sponsored by SAMRC was completed for Ad26.COV2.S.

Study VAC31518COV3012 (Sisonke [Together])

This was a Phase 3b, open-label, single-arm, multicentre, implementation Study to evaluate the effectiveness of the single-dose of Ad26.COV2.S among 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.

Safety Summary

Among 477,234 participants who received the single Ad26.COV2.S.dose, 10,279 AEs were reported, of which 138 (1.3%) were SAEs or AESI. Women reported more AEs than men (2.3% versus 1.6%). AE reports decreased with increasing age (3.2% for age 18 to 30 years, 2.1% for age 31 to 45 years, 1.8% for age 46 to 55 years, and 1.5% for age >55 years). Participants with previous COVID-19 infection reported slightly more AEs (2.6% versus 2.1%). The most common reactogenicity events were headache (n=4,923) and body aches (n=4,483), followed by injection site pain (n=2,767) and fever (n=2,731), and most occurred within 48 hours of vaccination. Two cases of thrombosis with thrombocytopenia syndrome and 4 cases of Guillain-Barré syndrome were reported post-vaccination. Most SAEs and AESI (n=138) occurred at lower than the expected population rates. Vascular (n=37; 39.1/100,000 PY) and nervous system disorders (n=31; 31.7/100,000 PY), immune system disorders (n=24; 24.3/100,000 PY), and infections and infestations (n=19; 20.1/100,000 PY) were the most common reported SAE categories.

Overall, the single dose of Ad26.COV2.S was well tolerated, effective at preventing severe COVID-19 infection and immunogenic among healthcare workers in South Africa, including PLWH.

9.1.2. Ongoing Clinical Studies

During the PBRER reporting interval, 7 interventional clinical studies sponsored by other organisations/institutions were ongoing for Ad26.COV2.S: 1 interventional clinical study (COV-BOOST [VAC31518COV2009]) sponsored by University Hospital Southampton NHS Foundation Trust; 1 interventional clinical study (VAC31518COV2012) sponsored by Vaccine

Trial Centre (Hospital for Tropical Diseases, Mahidol University, Thailand); 1 interventional clinical study (VAC31518COV2016 [AUR1-8-341]) sponsored by The Aurum Institute NPC; 1 interventional clinical study (VAC31518COV3018) sponsored by Mayo Clinic; 1 interventional clinical study (VAC31518COV3021 [Sisonke Boost Open-Label Study {SISONKE2}]) sponsored by SAMRC; 1 interventional clinical study (VAC31518COV4012) sponsored by 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 National Institute of Health.

The summary of safety findings from these ongoing clinical studies are presented below:

Study COV-BOOST (VAC31518COV2009)

This is a Phase 2, randomised, multicentre study conducting in the 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 enrolled in 2 or 3 stages.

At the time of DLD of this PBRER, 2,878 participants were enrolled, of which 206 received Ad26.COV2.S.

During the reporting interval, no relevant safety information related to Ad26.COV2.S from this clinical study became available.

Study VAC31518COV2012

This is a 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 570 participants were recruited. Enrolment of groups are open-label allocation and assessor masked.

At the time of DLD of this PBRER, 514 participants were assessed for eligibility and 465 participants received the Ad26.COV2.S in this study.

During the reporting interval, no new significant 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 study of the safety and immunogenicity of COVID-19 vaccine strategies in 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 enrolled 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 DLD of this PBRER, 231 participants received Ad26.COV2.S in this study.

During the reporting interval, no new significant safety findings related to Ad26.COV2.S from this clinical study became available.

Study VAC31518COV3018

This is a Phase 3, prospective, open-label clinical study 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 DLD of this PBRER, 55 participants received Ad26.COV2.S in this study.

During the PBRER reporting interval, no new significant 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 is being 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 DLD of this PBRER, 250,878 participants received Ad26.COV2.S in this study.

During the reporting interval, no new significant safety findings related to Ad26.COV2.S from this clinical study became available.Refer to Section 8, Findings from Noninterventional Studies, for more information about booster vaccine effectiveness from this study.

Study VAC31518COV4012

This is a study in participants >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 Ad26.COV2.S and boosting with either Ad26.COV2.S or 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 and boosting with either Ad26.COV2.S or mRNA vaccines.

At the time of DLD of this PBRER, 298 participants received Ad26.COV2.S in this study.

During the reporting interval, no new significant 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 DLD of this PBRER, 150 participants received Ad26.COV2.S in this study.

During the reporting interval, no significant 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 interval 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 interval, which coded to the Standardised MedDRA Query (SMQ) Medication errors (broad)[13], provided in Appendix 5.

Results/Discussion

During this reporting interval, a total of 14 (13 medically confirmed and 1 medically unconfirmed) initial, primary dose cases reporting medication errors were retrieved. There were 3 serious and 11 nonserious cases which reported a total of 17 medication error events of interest (EOI) (2 serious; 15 nonserious).

During this reporting interval, a total of 17 (9 medically confirmed and 8 medically unconfirmed) post-marketing, initial cases reported as booster dose were identified. Of these 17 cases, there were

[13] 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 itself 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.

14 serious and 3 nonserious cases, which reported a total of 17 medication error EOI (11 serious; 6 nonserious). Of these cases, 14 were heterologous and 3 were homologous.

Post-marketing Sources (Including Spontaneous and Solicited) Cases

Primary Dose

During this reporting interval, a total of 14 (13 medically confirmed and 1 medically unconfirmed) post-marketing, initial, primary dose cases reporting medication errors were retrieved. Of these 14 cases, 5 concerned paediatric patients and are discussed in Subsection 9.2.1, Paediatric Cases below. The remaining 9 cases reported 12 medication error EOI (2 serious; 10 nonserious) and are presented below.

Cumulatively, 2,520 (1,798 medically confirmed and 722 medically unconfirmed) post-marketing, primary dose cases reporting medication errors were retrieved. Of these 2,520 cases, 377 concerned paediatric patients which are discussed in Subsection 9.2.1, Paediatric Cases below. The remaining 2,143 cases reported a total of 2,883 EOI (37 serious; 2,846 nonserious) of medication error are presented below.

An overview of these cases is presented in Table 11.

Table 11: Characteristics of Selected Cases Involving the Use of Ad26.COV2.S and Reporting Medication Errors

Case Characteristics		Number of Cases Received During the Reporting interval=9	Number of Cases Received Cumulatively=2,143[a]
Sex	Male	2	714
	Female	3	690
	NR	4	739
Age (Years)[b]	18 to 35	2	322
Minimum: 24	36 to 50	1	303
Maximum:63	51 to 64	2	354
Mean: 44	Adult	1	41
Median: 48	NR	3	930
Sources	Spontaneous	8	2,129
	Clinical study (noninterventional, solicited)	1	14
Country/Territory	United States	5	1,838
	United Kingdom	2	4
	Netherlands	1	11
	South Africa	1	6
Event Characteristics		**Number of Events=12**	**Number of Events= 2,883**
Seriousness (Event Level)[c]	Nonserious	10	2,846
	Serious	2	37
Outcome (Event Level)[c]	Resolved	1	50
	NR	11	2,791

Table 11: Characteristics of Selected Cases Involving the Use of Ad26.COV2.S and Reporting Medication Errors

Key: EOI=Event(s) of Interest; NR=Not Reported
a: For the cumulative column, the counts were presented in decreasing order based on the current reporting interval (25 February 2023 to 24 February 2024).
b: The median and mean age calculation were based on the current reporting interval (25 February 2023 to 24 February 2024). Age group was presented for cases where age was not reported.
c: Seriousness and outcome have been presented for the EOI. A single case may report more than 1 EOI.

Of these 9 post-marketing, primary dose cases received during the reporting interval, the most frequently reported country/territory of origin was US (n=5). These cases concerned 2 males, 3 females, and 4 did not report sex. The age range was from 24 to 63 years.

The frequency distribution of the MedDRA PTs of interest reported in cases (n=9) is presented in Table 12. A single case may contain more than 1 EOI.

Majority of the cases included the PT of Poor quality product administered, and 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 Cases Reporting Medication Errors With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Reporting Interval[a]		Number of Events Reported Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
Poor quality product administered	0	3	0	712
Product storage error	0	2	2	596
Expired product administered	0	1	4	541
Incorrect dose administered	0	1	2	103
Medication error	1	0	2	119
Overdose	1	0	4	60
Product administration error	0	1	2	66
Product dose omission issue	0	1	0	5
Product temperature excursion issue	0	1	0	42

Key: EOI=Event(s) of Interest; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: The MedDRA PTs of interest were sorted by decreasing order for the current reporting interval (25 February 2023 to 24 February 2024). A single case may report more than 1 EOI.
b: For the cumulative column, the events were presented in decreasing order based on the event counts of the current reporting interval (25 February 2023 to 24 February 2024).

Of the 9 post-marketing, primary dose cases retrieved during the reporting interval, none of the cases reported the PT of Off-label use.

The majority (55.6%; 5/9) of the cases involved medication errors without any additional AEs reported (classified as medication errors without harm); whereas 44.4% (4/9) of cases reported medication errors with harm. These 4 cases reported 38 additional AEs (6 serious; 32 nonserious). The reported events of medication errors in these cases were medication error, overdose, product administration error, and product dose omission issue (n=1 each).

The frequency distribution of additional AEs reported in 4 cases reporting medication errors with harm with the use of Ad26.COV2.S is presented in Table 13. Most of the AEs were nonserious and presented local and systemic reactogenicity to Ad26.COV2.S. Serious AEs included headache, herpes zoster, and injection site pain.

Table 13: Frequency Distribution of Additional AEs in Cases Involving the Use of Ad26.COV2.S and Reporting Medication Errors With Harm

Additional AEs	Number of Events Received During the Reporting Interval[a]		Number of Events Received Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
Headache	1	1	11	100
Herpes zoster	1	1	1	1
Injection site pain	1	1	4	59
Anaphylactic reaction	1	0	5	0
Arthralgia	0	1	4	31
Chills	0	1	4	66
Cough	0	1	4	11
COVID-19	1	0	6	10
Diarrhoea	0	1	5	18
Dizziness	0	1	7	30
Fatigue	0	1	11	81
Hyperpyrexia	1	0	1	0
Injection site discomfort	0	1	0	2
Injection site erythema	0	1	0	8
Injection site haematoma	0	1	0	3
Injection site hypoaesthesia	0	1	0	3
Injection site induration	0	1	0	1
Injection site inflammation	0	1	0	2
Injection site paraesthesia	0	1	0	3
Injection site pruritus	0	1	0	2
Injection site reaction	0	1	0	5
Injection site swelling	0	1	0	5
Injection site warmth	0	1	0	4
Lymphadenopathy	0	1	0	8
Malaise	0	1	3	18
Myalgia	0	1	4	37
Nasopharyngitis	0	1	0	6
Nausea	0	1	4	43
Oropharyngeal pain	0	1	1	12
Pain in extremity	0	1	8	76
Paraesthesia	0	1	3	25

Table 13: Frequency Distribution of Additional AEs in Cases Involving the Use of Ad26.COV2.S and Reporting Medication Errors With Harm

Additional AEs	Number of Events Received During the Reporting Interval[a]		Number of Events Received Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
Pruritus	0	1	0	5
Pyrexia	0	1	7	89
Suspected COVID-19	0	1	2	10
Vomiting	0	1	2	15

Key: AE=Adverse Event; COVID-19=Coronavirus Disease 2019
a: The AEs are sorted by decreasing order for the current reporting interval (25 February 2023 to 24 February 2024). A single case may report more than 1 AE.
b: For the cumulative column, the events were presented in decreasing order based on the event counts of the current reporting interval (25 February 2023 to 24 February 2024).

Booster Dose

During this reporting interval, a total of 17 (9 medically confirmed and 8 medically unconfirmed) post-marketing, initial cases reported as booster dose were identified. Of these 17 cases, none concerned paediatric patients. These 17 booster cases reported 17 EOI (11 serious; 6 nonserious) of medication errors.

Cumulatively, 1,096 (291 medically confirmed and 805 medically unconfirmed) post-marketing cases reported as booster dose were identified. Of these 1,096 cases, 7 concerned paediatric patients and are discussed in the subsection below. The remaining 1,089 booster cases reported a total of 1,139 mediation error EOI (32 serious; 1,107 nonserious) and are presented below.

An overview of these cases is presented in Table 14.

Table 14: Characteristics of Selected Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Medication Errors

Case Characteristics		Number of Cases Received During the Reporting Interval=17	Number of Cases Received Cumulatively=1,089[a]
Sex	Male	10	512
	Female	6	532
	NR	1	45
Age (Years)[b]	18 to 35	4	218
Minimum: 24	36 to 50	1	268
Maximum: 74	51 to 64	6	188
Mean: 51.1	≥65	3	157
Median: 55	NR	3	248
Sources	Spontaneous	17	765
Country/Territory	Germany	10	39
	United States	3	460
	Philippines	1	3
	Poland	1	1
	Spain	1	5
	United Kingdom	1	1

Table 14: Characteristics of Selected Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Medication Errors

Case Characteristics		Number of Cases Received During the Reporting Interval=17	Number of Cases Received Cumulatively=1,089[a]
Classification	Heterologous	14	405
	Homologous	3	684
Event Characteristics		**Number of Events= 17**	**Number of Events= 1,139**
Seriousness (Event Level)[c]	Nonserious	11	1,107
	Serious	6	32
Outcome (Event Level)[c]	NR	17	1,122

Key: EOI=Event(s) of Interest; NR=Not Reported

a: For the cumulative column, the counts were presented in decreasing order based on the current reporting interval (25 February 2023 to 24 February 2024).

b: The median and mean age calculations were based on the current reporting interval (25 February 2023 to 24 February 2024).

c: Seriousness and outcome have been presented for the EOI. A single case may report more than 1 EOI.

Of these 17 post-marketing cases reported as booster dose received during the reporting interval, the most frequently reported country/territory of origin were Germany (n=10), followed by the US (n=3). These cases concerned 6 females, 10 males, and 1 did not report sex. The age range was from 24 to 74 years.

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

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

MedDRA PTs	Number of Events Reported During the Reporting Interval[a]		Number of Events Reported Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
Interchange of vaccine products	11	3	27	15
Incorrect dose administered	0	3	0	22

Key: EOI=Event(s) of Interest; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term

a: The MedDRA PTs of interest are sorted by decreasing order for the current reporting interval (25 February 2023 to 24 February 2024). A single case may report more than 1 EOI.

b: For the cumulative column, the events were presented in decreasing order based on the event counts of the current reporting interval (25 February 2023 to 24 February 2024).

As displayed in Table 15, the most frequently reported MedDRA PT of interest for this current reporting interval was Interchange of vaccine products (n=14). Of the 17 cases reported as booster dose, the majority (88.2%; 15/17) of them contained additional AEs (classified as medication errors with harm).

The frequency distribution of additional AEs (n≥2) reported in these cases is presented in Table 16. 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 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 Interval[a]		Number of Events Received Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
Drug ineffective	10	0	18	0
COVID-19	8	0	16	22
COVID-19 immunisation	0	3	1	9
Gait disturbance	0	2	1	4
Suspected COVID-19	2	0	4	11

Key: AE=Adverse Event; COVID-19=Coronavirus disease 2019; EOI=Event(s) of Interest

a: The AEs with a frequency ≥2 have been presented and sorted by decreasing order for the current reporting interval (25 February 2023 to 24 February 2024). A single case may report more than 1 EOI.

b: For the cumulative column, the events were presented in decreasing order based on the event counts of the current reporting interval (25 February 2023 to 24 February 2024).

9.2.1. Paediatric Cases

Post-marketing Sources (Including Spontaneous and Solicited) Cases

Primary Dose Case

During this reporting interval, a total of 5 medically confirmed (no medically unconfirmed) post-marketing, initial cases reporting medication errors in the paediatric population were retrieved. These 5 cases reported 5 nonserious EOI of medication errors and are presented below.

Cumulatively, 377 (199 medically confirmed and 178 medically unconfirmed) post-marketing, primary dose cases reporting medication error EOI in paediatric population were identified. There were 23 serious and 354 nonserious cases which reported a total of 406 medication error events (7 serious; 399 nonserious).

An overview of these cases is presented in Table 17.

Table 17: Characteristics of Selected Cases Involving the Use of Ad26.COV2.S and Reporting Medication Errors

Case Characteristics		Number of Cases Received During the Reporting Interval=5	Number of Cases Received Cumulatively=377[a]
Sex	Male	5	192
Age (Years)[b] **Minimum: 16** **Maximum:17** **Mean: 16.4** **Median: 16**	16 17	3 2	86 141
Sources	Spontaneous	5	373
Country/Territory	Portugal	5	12
Event Characteristics		**Number of Events=5**	**Number of Events=406**
Seriousness (Event Level)[c]	Nonserious	5	399
Outcome (Event Level)[c]	Resolved	1	1
	NR	4	404

Key: EOI=Event(s) of Interest; NR=Not Reported
a: For the cumulative column, the counts were presented in decreasing order based on the current reporting interval (25 February 2023 to 24 February 2024).
b: The median and mean age calculation were based on the current reporting interval (25 February 2023 to 24 February 2024). Age group was presented for cases where age was not reported.
c: Seriousness and outcome have been presented for the EOI. A single case may report more than 1 EOI.

All these 5 cases, post-marketing, primary dose, paediatric cases received during the reporting interval were from country of Portugal. All 5 cases concerned male patients. The reported ages were 16 (n=3) and 17 (n=2).

The frequency distribution of the MedDRA PTs of interest reported in paediatric cases is presented in Table 18. The most frequently reported medication error PT was Product administered to patient of inappropriate age (n=3).

Table 18: Frequency of MedDRA PTs of Interest in Cases Reporting Medication Errors in the Paediatric Population With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Interval Reporting interval		Number of Events Reported Cumulatively[a]	
	Serious	Nonserious	Serious	Nonserious
Product administered to patient of inappropriate age	0	3	3	345
Product use issue	0	1	0	21
Vaccination error	0	1	0	4

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: For the cumulative column, the events were presented in decreasing order based on the event counts of the current reporting interval (25 February 2023 to 24 February 2024).

Of the 5 post-marketing, primary dose paediatric cases retrieved during the reporting interval, none of the cases reported the PT of Off-label use. Of these 5 cases, 4 cases did not have additional AEs (classified as medication errors without harm) and 1 case contained additional AEs (20%, 1/5) (classified as medication errors with harm).

The frequency distribution of additional AEs reported in this case is presented in Table 19. The most frequently reported events were nonserious and represented local and systemic reactogenicity to Ad26.COV2.S and adverse reactions of hypersensitivity.

Table 19: Frequency Distribution of Additional AEs in Cases Reported as Booster Involving Use of Ad26.COV2.S and Reporting Medication Errors With Harm

Additional AEs	Number of Events Received During the Interval Reporting interval[a]		Number of Events Received Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
Headache	0	1	0	41
Pyrexia	0	1	2	45
Vomiting	0	1	0	4

Key: AE=Adverse Event

a: The AEs have been presented and sorted by decreasing order for the current reporting interval (25 February 2023 to 24 February 2024).

b: For the cumulative column, the events were presented in decreasing order based on the event counts of the current reporting interval (25 February 2023 to 24 February 2024).

Paediatric Booster Cases

During this reporting interval, there were no post-marketing, initial cases reported as booster which reported medication error events identified in the paediatric population.

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 7 cases, 1 was serious and 6 were nonserious, which reported a total of 10 EOI (All nonserious) of medication error.

Clinical Trial Cases

During this reporting interval, no primary dose clinical cases and no booster cases reporting medication error were retrieved from Janssen-Sponsored and Janssen-Supported Clinical Studies.

Janssen-Sponsored Clinical Studies

During this reporting interval, no cases reporting medication error related to the use of Ad26.COV2.S were retrieved from a Janssen-Sponsored Clinical Study.

Janssen-Supported Clinical Studies

During this reporting interval, no cases reporting medication error related to the use of Ad26.COV2.S were retrieved from a Janssen-Supported Clinical Study.

Line Listings

Death: During the current reporting interval (25 February 2023 to 24 February 2024), no fatal cases were retrieved.

Booster: A cumulative CIOMS II LL of cases reported as booster is presented in Appendix 7.1.

Discussion

Overall, the majority of primary dose cases with medication errors involved use of expired product, poor quality product or product that was stored inappropriately. Most of the primary dose cases did not report AEs. Of the booster cases, the majority reported the PT Interchange of vaccine products. Reported AEs in all cases with medication errors usually were nonserious, without evidence for a causal association of AEs to the reported errors. No safety concern arose from review of the paediatric initial and booster 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

The following non-clinical study was completed during the reporting interval. The exploratory transcriptomics analysis was considered not suitable and not reliable to explore possible TTS-related pathways based on numerous false positive hits in the huMMR treatment group in the study. Also, evaluation of VITT-related parameters in the same study, such as platelet counts, D-dimer and anti-PF4 and potentially VITT-associated anti-NAP2 antibodies, did not indicate any relevant changes in any of the experimental groups. Therefore, it was opted to not perform transcriptomic analysis of the remaining groups of the study, including the Ad26.COV2.S group (see Table 20).

Table 20: Overview of Completed Non-clinical Study With Focus on TTS for Ad26.COV2.S

Risk	Non-clinical Study Number	Non-clinical Study Title
Thrombosis with thrombocytopenia syndrome	TOX15258	Ad26.COV2.S (Prophylactic COVID-19 Vaccine): A Transcriptomics Exploratory Study in Cambodian Cynomolgus Monkey

Key: Ad26.COV2.S=Adenovirus Type 26 Coronavirus 2 Spike; COVID-19=Coronavirus Disease-2019; TTS=Thrombosis With Thrombocytopenia Syndrome

No new safety concerns were identified from non-clinical studies.

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 any active ingredient or combination for which Company is an MAH. It should be noted that the literature searches are wider than those for ICSR 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, Overview of Signals: New, Ongoing, or Closed and 16.3, Evaluation of Risks and New Information 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

Chang MS, Kim HR, Kim S, et al. Noninfectious Uveitis Risk After COVID-19 Vaccination: A Nationwide Retrospective Cohort Study. *Am J Ophthalmol.* 2024;258:22-31. doi:10.1016/j.ajo.2023.09.015

Purpose: To investigate the incidence and risk of noninfectious uveitis (NIU) following COVID-19 vaccination compared with an unvaccinated, uninfected control group.

Design: Retrospective population-based cohort study.

Methods: We included 5,185,153 individuals who received the first vaccine dose in the exposed group and 2,680,164 individuals in the unexposed, uninfected control group. The study observed for 180 days from their index date. Cumulative incidence and risk of NIU following COVID-19 vaccination, and attributable risk factors were assessed.

Results: Multivariable analysis showed elevated risk of nonanterior NIU within 60 days (hazard ratio [HR] 1.27 [95% confidence interval {CI} 1.03-1.55] and 61-180 days (HR 1.39 [95% CI 1.20-1.62]). Subgroup analysis highlighted an increased risk in females for early and delayed nonanterior uveitis (HR 1.44 [95% CI 1.08-1.92]; HR 1.78 [95% CI 1.43-2.20], respectively). Regardless of the location

and onset timing of uveitis, a history of NIU was identified as the most significant risk factor, with a high hazard ratio ranging from 100 to 200.

Conclusion: COVID-19 vaccination may modestly increase the risk of nonanterior uveitis especially in females. Despite adjustments, bias may persist in the exposed group, owing to significant differences between unexposed and exposed groups and low incidence of nonanterior uveitis in the unexposed group. Future research should aim to refine these findings by assessing uveitis risk in prior NIU patients and by enlarging the sample size or cohort matching.

Company Comment: *A subgroup analysis by vaccine type demonstrated that the highest cumulative incidence of uveitis was associated with the ChAdOX1 vaccine, followed by BNT162b2, mRNA-1273, and Ad26.COV2.S. However, in line with the authors' acknowledgment of potential biases, note is made that at baseline, risk factors for noninfectious uveitis (including but not limited to autoimmune diseases, diabetes mellitus, and recent intraocular surgery) (Rim 2018; Joltikov 2021) were more prevalent in the vaccine-exposed group than controls; these differences were both statistically and clinically significant.*

Although the study sample was considered by the authors "[...]representative of the entire Korean adult population", it cannot be generalisable to other populations worldwide. Additionally, the GMS data cumulative to 23 January 2024 was retrieved, and analysed the identified 26 cases of iris and uveal tract infections, irritations, and inflammations. No new safety information is detected at this time.

Duijster JW, Schoep ME, Nieboer TE, et al. Menstrual abnormalities after COVID-19 vaccination in the Netherlands: A description of spontaneous and longitudinal patient-reported data. *Br J Clin Pharmacol*. 2023;89(10):3126-3138. doi: 10.1111/bcp.15799

Purpose: During the COVID-19 vaccination campaigns, the number of reports of menstrual abnormalities increased rapidly. Here, we describe the nature and potential risk factors associated with menstrual abnormalities based on spontaneously reporting data as well as data from a prospective cohort event monitoring (CEM) study as these are poorly studied.

Methods: Reports of menstrual abnormalities received by the Netherlands Pharmacovigilance Centre Lareb in the spontaneous reporting system between February 2021 and April 2022 were summarized. In addition, logistic regression analysis was performed on the reported menstrual abnormalities in the CEM study to assess the association between person characteristics, prior SARS-CoV-2 infection and use of hormonal contraceptives and the occurrence of menstrual abnormalities after vaccination.

Results: We analysed over 24 000 spontaneous reports of menstrual abnormalities and over 500 episodes (among 16 929 included women) of menstrual abnormalities in the CEM study. The CEM study showed an incidence of 41.4 per 1000 women aged ≤54 years. Amenorrhoea/oligomenorrhoea and heavy menstrual bleeding collectively accounted for about half of all abnormalities reported. Significant associations were observed for the age group 25-34 years (odds ratio 2.18; 95% confidence interval 1.45-3.41) and the Pfizer vaccine (odds ratio 3.04; 95% confidence interval 2.36-3.93). No association was observed for body mass index and presence of most comorbidities assessed.

Conclusion: The cohort study showed a high incidence of menstrual disorders among women aged ≤54 years, and this observation was supported by the analysis of spontaneous reports. This suggests that a relation between COVID-19 vaccination and menstrual abnormalities is plausible and should be further investigated.

Company Comment: *The authors reported that the study identified "the highest" reporting rates for all menstrual abnormalities together for the Johnson &Johnson vaccine (523.0 per 100,000 vaccinations) stating that "[...]this corresponds to a ratio of 1 in 200 female recipients of the Johnson*

&Johnson vaccine who reported a menstrual abnormality to Lareb". In addition,"[...]over 500 menstrual abnormalities were recorded by participants in the CEM study among 16,929 included women. [...] The incidences of amenorrhoea/oligomenorrhoea and irregular blood loss exceeded 10 per 1000 vaccinated women (aged<65 years) for Johnson & Johnson, Moderna and Pfizer vaccines, while the incidence of heavy menstrual bleeding exceeded 10 per1000 vaccinated women only for the Moderna and Pfizer vaccines."

The systemic immune response including hormonal and inflammatory pathways was mentioned by the authors as a potential mechanism. In addition, they also emphasised a different immune activity in the first and second part of the menstrual cycle, stating "[...] most menstrual abnormalities were found in women who were vaccinated in the second part of their menstrual cycle, after ovulation."

A signal on "Heavy menstrual bleeding" and "Menstrual cycle and uterine bleeding disorders and postmenopausal haemorrhage" has been previously opened twice but the safety issue was not confirmed. Nevertheless, considering several limitations in both the spontaneous reporting system and the CEM study, lack of detailed data and the analysis that would elucidate the mechanism of these adverse reactions, there is no safety signal identified at this time.

Han JY, Kim S, Han J, et al. Neuro-ophthalmic adverse events of COVID-19 infection and vaccines: A nationwide cohort study. *Invest Ophthalmol Vis Sci.* 2023;64(14):37. doi: 10.1167/iovs.64.14.37

Purpose: To evaluate the association of COVID-19 infection and vaccination with neuro-ophthalmic adverse events.

Methods: In this nationwide population-based retrospective cohort study, 8,498,353 patients were classified into three groups: control, COVID-19 infection, and COVID-19 vaccination. We conducted separate analyses for the early phase (within 60 days) and late phases (61-180 days) to estimate the incidence rates and hazard ratio (HR) for each neuro-ophthalmic adverse event. The adverse events included in this analysis were optic neuritis, papilledema, ischemic optic neuropathy, third nerve palsy, fourth nerve palsy, sixth nerve palsy, facial palsy, nystagmus, ptosis, blepharospasm, anomalies of pupillary function, and Guillain-Barré syndrome/Miller Fisher syndrome (GBS/MFS).

Results: Neuro-ophthalmic adverse events other than ptosis and GBS/MFS exhibited no significant increase after COVID-19, and their incidence was extremely low. The incidence rate of ptosis in both phases was significantly higher in patients administered COVID-19 vaccination (HR = 1.65 in the early phase and HR = 2.02 in the late phase) than in the control group. Additionally, BNT162b2 conferred a lower ptosis risk than ChAdOx1. GBS/MFS had a significantly higher incidence rate in the early phase (HR = 5.97) in patients with COVID-19 infection than in the control group.

Conclusion: Ptosis was associated with COVID-19 vaccination, particularly with the ChAdOx1 vaccine, while GBS/MFS was associated with COVID-19 infection. In contrast, no association was found between other neuro-ophthalmic adverse events and COVID-19 infection or vaccination. These results may provide helpful insights for diagnosing and treating the neuro-ophthalmological adverse events after COVID-19.

Company Comment: *The authors conducted a population-based retrospective cohort study, in which patients were classified into 3 groups: control, COVID-19 infection, and COVID-19 vaccination to identify incidence rate of neuro-ophthalmic adverse events. As mentioned by the authors, "[...]the ChAdOX1 vaccine was strongly associated with ptosis". In the context of the Ad26.COV2.S vaccine, and using the ChAdOx1 vaccine as a reference, Ad26.COV2.S showed a significant negative association with ptosis (HR = 0.41 [95% CI, 0.22 to 0.77]; P = 0.006). Given the negative findings specific to Ad26.COV2.S, no new safety information is detected at this time.*

Nahab F, Bayakly R, Sexton ME, et al. Factors associated with stroke after COVID-19 vaccination: a statewide analysis. *Front Neurol.* 2023 Jun 28;14:1199745. Published 2023 Jun 28. doi:10.3389/fneur.2023.1199745.

Purpose: The objective of our study was to evaluate vaccine type, COVID-19 infection, and their association with stroke soon after COVID-19 vaccination.

Methods: In a retrospective cohort study, we estimated the 21-day post-vaccination incidence of stroke among the recipients of the first dose of a COVID-19 vaccine. We linked the Georgia Immunization Registry with the Georgia Coverdell Acute Stroke Registry and the Georgia State Electronic Notifiable Disease Surveillance System data to assess the relative risk of stroke by the vaccine type.

Results: Approximately 5 million adult Georgians received at least one COVID-19 vaccine between 1 December 2020 and 28 February 2022: 54% received BNT162b2, 41% received mRNA-1273, and 5% received Ad26.COV2.S. Those with concurrent COVID-19 infection within 21 days post-vaccination had an increased risk of ischemic (OR = 8.00, 95% CI: 4.18, 15.31) and hemorrhagic stroke (OR = 5.23, 95% CI: 1.11, 24.64) with no evidence for interaction between the vaccine type and concurrent COVID-19 infection. The 21-day post-vaccination incidence of ischemic stroke was 8.14, 11.14, and 10.48 per 100,000 for BNT162b2, mRNA-1273, and Ad26.COV2.S recipients, respectively. After adjusting for age, race, gender, and COVID-19 infection status, there was a 57% higher risk (OR = 1.57, 95% CI: 1.02, 2.42) for ischemic stroke within 21 days of vaccination associated with the Ad26.COV2.S vaccine compared to BNT162b2; there was no difference in stroke risk between mRNA-1273 and BNT162b2.

Conclusion: Concurrent COVID-19 infection had the strongest association with early ischemic and haemorrhagic stroke after the first dose of COVID-19 vaccination. Although not all determinants of stroke, particularly comorbidities, were considered in this analysis, the Ad26.COV2.S vaccine was associated with a higher risk of early post-vaccination ischemic stroke than BNT162b2.

Company Comments: *According to the study results, "the 21-day post-vaccination incidence of ischaemic stroke was 8.14, 11.14, and 10.48 per 100,000 for BNT162b2, mRNA-1273 and Ad26.COV2.S recipients, respectively. After adjusting for age, race, gender, and COVID-19 infection status there was a 57% higher risk (OR=1.57, 95% CI: 1.02, 2.42) for ischaemic stroke within 21 days of vaccination associated with the Ad26.COV2.S vaccine compared to BNT162b2." The authors indicated that "concurrent COVID-19 infection had the strongest association with early ischaemic and haemorrhagic stroke after first dose COVID-19 vaccination", though with no evidence for interaction between vaccine type. "The Ad26.COV2.S vaccine was associated with a higher risk of early post-vaccination ischaemic stroke than BNT162b2."*

No information on patients' comorbidities, concomitant medications, examination and diagnostic details were presented in the study. Among the limitations, retrospective nature of the study and the increased use of home COVID-19 tests that may contribute to an underreporting of COVID-19 infection as well as unavailable data to determine if any of these early post-vaccination strokes were related to thrombotic thrombocytopaenia. Hence, given the limited information, there is no new safety information detected at this time.

11.2. Class Effect Literature

Yoo H, Kim SY, Park MS, et al. COVID-19 Vaccine-Associated Pneumonitis in the Republic of Korea: A Nationwide Multicenter Survey. *J Korean Med Sci.* 2023;38(14):e106. Published 2023 Apr 10. doi:10.3346/jkms.2023.38.e106.

Recent reports have suggested that pneumonitis is a rare complication following vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). However, its clinical features and

outcomes are not well known. The aim of this study was to identify the clinical characteristics and outcomes of patients with vaccine-associated pneumonitis following vaccination against SARS-CoV-2.

Methods: In this nationwide multicenter survey study, questionnaires were distributed to pulmonary physicians in referral hospitals. They were asked to report cases of development or exacerbation of interstitial lung disease (ILD) associated with the coronavirus disease 2019 vaccine. Vaccine-associated pneumonitis was defined as new pulmonary infiltrates documented on chest computed tomography within 4 weeks of vaccination and exclusion of other possible etiologies.

Results: From the survey, 49 cases of vaccine-associated pneumonitis were identified between February 27 and October 30, 2021. After multidisciplinary discussion, 46 cases were analyzed. The median age was 66 years and 28 (61%) were male. The median interval between vaccination and respiratory symptoms was 5 days. There were 20 (43%), 17 (37%), and nine (19%) patients with newly identified pneumonitis, exacerbation of pre-diagnosed ILD, and undetermined pre-existing ILD, respectively. The administered vaccines were BNT162b2 and ChAdOx1 nCov-19/AZD1222 each in 21 patients followed by mRNA-1273 in three, and Ad26.COV2.S in one patient. Except for five patients with mild disease, 41 (89%) patients were treated with corticosteroid. Significant improvement was observed in 26 (57%) patients including four patients who did not receive treatment. However, ILD aggravated in 9 (20%) patients despite treatment. Mortality was observed in eight (17%) patients.

Conclusion: These results suggest pneumonitis as a potentially significant safety concern for vaccines against SARS-CoV-2. Clinical awareness and patient education are necessary for early recognition and prompt management. Additional research is warranted to identify the epidemiology and characterize the pathophysiology of vaccine-associated pneumonitis.

Company Comment: *According to the study results, "There were 20 (43%), 17 (37%), and 9 (19%) patients with newly identified pneumonitis, exacerbation of pre-diagnosed ILD, and undetermined pre-existing ILD, respectively. The administered vaccines were BNT162b2 and ChAdOx1 nCov-19/AZD1222 each in 21 patients followed by mRNA-1273 in 3 and Ad26.COV2.S in 1 patient. Half of the patients (54%) experienced development or exacerbation of ILD after the first dose of vaccination." The authors mentioned that there were no significant differences in clinical characteristics and outcomes between patients who received mRNA vaccines and vector-based vaccines. Of the seven deceased patients, "pneumonitis occurred in one patient after the second dose of ChAdOx1 nCov-19 and the patient died of respiratory failure due to the progression of pneumonitis." Two patients with pre-diagnosed ILD experienced an exacerbation of ILD following the second dose of BNT162b2 leading to respiratory failure. Vaccination with the second dose of ChAdOx1 nCov-19/AZD1222 led to exacerbation of ILD in a patient and the patient died from hospital-acquired pneumonia. In other 3 deceased patients who received the second dose of ChAdOx1 nCov-19, the death occurred from "hospital-acquired pneumonia, sepsis or intracranial haemorrhage."*

Among the potential mechanisms of pneumonitis associated with the COVID-19 vaccine, the authors discussed "immune-mediated injuries, especially T cell-mediated reactions" as well as "vaccine-induced autoimmunity". Nevertheless, taking into consideration the study limitations, such as "no single confirmative test for the diagnosis of vaccine-associated pneumonitis", the frequency of the vaccines used at the timepoint (BNT162b2 was the most administered followed by ChAdOx1 nCov-19), potential selection bias including only severe cases, not generalisability of the study population limited to the Korea ILD Study Group, retrospective nature of the study including limited COVID infection testing as well as the possibility of underestimation of vaccine-associated pneumonitis by limiting the time interval to 4 weeks especially "if potential pathophysiology is due to autoimmunity", there is no new safety information identified 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 Concerns/ Variants Of Interest (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 the 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]: 58.9% [43.40; 70.50] 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 (<37%). 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 61% 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 remain 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.

Overall, there is no safety concern related to lack of efficacy.

14. LATE-BREAKING INFORMATION

Since the DLD of 24 February 2024, no late-breaking information has been identified regarding Ad26.COV2.S.

15. OVERVIEW OF SIGNALS: NEW, ONGOING, OR CLOSED

A tabulation of validated safety signals new, ongoing, and closed during the reporting interval can be found in Appendix 3. Open signals at DLD are discussed in Section 15.1, Ongoing Signals; closed signals are discussed in Section 16.2.1, Closed Signals.

15.1. Ongoing Signals

There were no signals that were undergoing evaluation at data-lock date of this report.

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

The topic of cutaneous vasculitis was closed in February 2023 and an Ad hoc report was submitted with the previous PBRER reporting interval 25 August 2022 and 24 February 2023 (JNJ- 78436735 [Ad26.COV2.S] Vaccine PBRER 2023). This topic was sufficiently addressed in the previous PBRER with DLD 24 February 2023 hence will not be discussed in the current PBRER.

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 of Risks and New Information and those relevant to specific AESI will be discussed under the relevant AESI subsection within Section 16.3.6, Adverse Events of Special Interest.

One trial to specifically evaluate the co-administration of Ad26.COV.S with influenza vaccines was conducted (Trial VAC31518COV3005). This was a Phase 3, randomised, double-blind, parallel, multicentre trial to evaluate safety, reactogenicity, and immunogenicity of Ad26.COV2.S co administered with a quadrivalent standard-dose in participants 18 years and above (≥18 to ≤64 years) or high-dose seasonal influenza vaccine in participants 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. Overall, the safety and reactogenicity profile of concomitant administration of Ad26.COV2.S and the standard dose or high dose influenza vaccine is considered acceptable. There were no safety concerns identified from this trial during the reporting interval. (See Section 7.1, Completed Clinical Trials).

Methods

The Company global safety database was searched for medically confirmed and medically unconfirmed cases received during this reporting interval and cumulatively which coded to the search criteria provided in Appendix 5.

Results/Discussion

Post-marketing Sources Cases

Primary Dose

During this reporting interval, a total of 8 (4 medically confirmed and 4 medically unconfirmed) post-marketing sources (including spontaneous and solicited), initial, primary dose cases reporting the use with concomitant vaccination were identified. There were 2 serious and 6 nonserious cases which reported a total of 30 events (4 serious, 26 nonserious).

Cumulatively, 122 (37 medically confirmed and 85 medically unconfirmed) post-marketing, primary dose cases reporting the use with concomitant vaccination were identified. There were 55 serious and 67 nonserious cases which reported a total of 618 events (192 serious, 426 nonserious).

The most frequently reported coadministered vaccine type (both during the reporting interval as well as cumulatively) was the influenza vaccine (interval n=4; cumulatively n=74). An overview of these cases is presented in Table 21.

Table 21: Characteristics of Post-marketing Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Concomitant Vaccination

Case Characteristics		Number of Cases Received During the Reporting Interval=8	Number of Cases Received Cumulatively=122[a]
Sex	Female	7	71
	Male	1	47
Age (Years)[b]	18 to 35	1	24
Minimum: 32	36 to 50	2	24
Maximum: 74	51 to 64	1	36
Mean: 53.2	≥65	2	29
Median: 51.5	Adult	2	3
Source	Spontaneous	4	103
	Clinical study (noninterventional, solicited)	3	14
	Clinical study (noninterventional, unsolicited)	1	4
Country/Territory	Netherlands	3	20
	France	2	3
	Brazil	1	15
	Germany	1	6
	United States	1	53

Table 21: Characteristics of Post-marketing Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Concomitant Vaccination

Event Characteristics		Number of Events=30	Number of Events=618
Seriousness (Event Level)[c]	Serious	4	192
	Nonserious	26	426
Outcome (Event Level)[c]	Not resolved	7	166
	Resolved	6	125
	Resolving	1	116
	NR	16	189
Concomitant Vaccine Type[d]	Influenza vaccine	4	74
	Hepatitis B vaccine	2	13
	Pertussis vaccine	2	2
	Pneumococcal vaccine	2	9

Key: NR=Not Reported

a: For the cumulative column, the counts were presented in decreasing order based on the current reporting interval (25February 2023 to 24 February 2024).

b: The median and mean age calculations were based on the current reporting interval (25 February 2023 to 24 February 2024). Age group was presented for cases where age was not reported.

c: Seriousness and outcome have been presented for all events. A single case may report more than 1 event.

d: Concomitant vaccines were presented in decreasing order for the current reporting interval (25 February 2023 to 24 February 2024). A single case may report more than 1 concomitant vaccine.

Of these 8 cases received, the most frequently (≥2) reported countries/territories of origin were the Netherlands (n=3), and France (n=2). The cases concerned 7 females, and 1 male. The age range was from 32 to 74 years.

The frequency distribution of the MedDRA PTs reported is presented in Table 22.

Table 22: Frequency Distribution of MedDRA PTs in Post-marketing Primary Dose Cases Reporting Concomitant Vaccination With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Reporting Interval[a]		Number of Events Reported Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
Exposure during pregnancy	0	2	1	2
Nasopharyngitis	0	2	0	3
Back pain	0	1	2	5
Bone contusion	0	1	0	1
Chronic obstructive pulmonary disease	0	1	0	1
Contusion	0	1	0	1
Cough	0	1	1	5
Depression	0	1	0	2
Erysipelas	1	0	1	0
Fall	0	1	0	1
Fatigue	0	1	1	21
Headache	0	1	0	22
Illness	0	1	0	3
Inappropriate schedule of product	0	1	1	2

Table 22: Frequency Distribution of MedDRA PTs in Post-marketing Primary Dose Cases Reporting Concomitant Vaccination With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Reporting Interval[a]		Number of Events Reported Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
administration				
Influenza	0	1	0	5
Libido disorder	0	1	0	1
Ligament sprain	0	1	0	1
Malaise	0	1	0	15
Muscle spasms	0	1	0	2
Neuromyelitis optica spectrum disorder	1	0	1	0
Premature labour	0	1	0	1
Pulmonary embolism	1	0	5	0
Pulmonary hypertension	1	0	1	0
Sinusitis	0	1	0	2
Skin laceration	0	1	0	1
Tinnitus	0	1	0	1
Upper respiratory tract infection	0	1	0	1
Urinary tract infection	0	1	0	1

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

a: The MedDRA PTs have been presented and sorted by decreasing order for the reporting interval (25 February 2023 to 24 February 2024). A single case may report more than 1 MedDRA PT.

b: For the cumulative column, the events were presented in decreasing order based on the event counts of the current reporting interval (25 February 2023 to 24 February 2024).

The events (≥2) included exposure during pregnancy and nasopharyngitis (n=2, each). Two cases reporting exposure during pregnancy are discussed further in Section 16.3.5.1, Use During Pregnancy. The mean and median TTO of all events were 188.9 and 171 days, respectively, and the range was from 0 to 637 days. Of the 30 events, 14 reported outcomes for events and are as follows: not resolved (n=7), resolved (n=6) and resolving (n=1).

Of the 8 post-marketing cases reported, 2 had partial dates of concomitant vaccine administration specified. Dates of vaccination were not specified for the remaining 6 cases. An overview of these cases is included in Table 23.

Table 23: Overview of MedDRA PTs in Post-marketing Primary Dose Cases Reporting Concomitant Vaccinations With the Use of Ad26.COV2.S (Cases=8)

MedDRA PTs	Number of Events[a]
Cases Reporting Specified Dates of Concomitant Vaccine Administration (n=2)	
Inappropriate schedule of product administration	1
Influenza	1
Malaise	1
Cases Reporting Unspecified Dates of Concomitant Vaccine Administration (n=6)[b]	
Exposure during pregnancy	2
Nasopharyngitis	2

Key: MedDRA=Medical Dictionary for Regulatory Activities; n=Number of Cases; PT=Preferred Term
a: A single case may report more than 1 MedDRA PT.
b: MedDRA PTs with frequency ≥2 have been presented.

Booster Dose

During this reporting interval, a total of 13 (all medically unconfirmed) post-marketing, initial cases reported as booster were identified. There were 3 serious and 10 nonserious cases which reported a total of 83 events (10 serious, 73 nonserious). All 13 cases were heterologous.

Cumulatively, 106 (16 medically confirmed and 90 medically unconfirmed) post-marketing cases reported as booster were identified. There were 33 serious and 73 nonserious cases which reported a total of 645 events (95 serious, 550 nonserious). Of these cases, 70 were heterologous and 36 were homologous.

The most frequently reported coadministered vaccine type (both during the reporting interval as well as cumulatively) was the influenza vaccine (interval n=13; cumulatively n=102).

An overview of these cases is presented in Table 24.

Table 24: Characteristics of Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Concomitant Vaccination

Case Characteristics		Number of Cases Received During the Reporting Interval=13	Number of Cases Received Cumulatively=106[a]
Sex	Female	6	54
	Male	6	49
	NR	1	3
Age (Years)[b]	18 to 35	2	13
Minimum: 21	36 to 50	4	18
Maximum: 77	51 to 64	3	35
Mean: 51.3	≥65	3	27
Median: 52	NR	1	9
Source	Clinical study (noninterventional, solicited)	9	39
	Spontaneous	4	64

Table 24: Characteristics of Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Concomitant Vaccination

Case Characteristics		Number of Cases Received During the Reporting Interval=13	Number of Cases Received Cumulatively=106[a]
Country/Territory	Germany	10	29
	United States	3	31
Classification	Heterologous	13	70
Event Characteristics		**Number of Events=83**	**Number of Events=645**
Seriousness (Event Level)[c]	Nonserious	73	550
	Serious	10	95
Outcome (Event Level)[c]	Resolving	38	172
	Not Resolved	18	111
	Resolved	16	184
	Recovered/resolved with sequelae	2	2
	NR	9	174
Concomitant Vaccine Type	Influenza vaccine	13	102

Key: NR=Not Reported

a: For the cumulative column, the counts were presented in decreasing order based on the current reporting interval (25 February 2023 to 24 February 2024).

b: The median and mean age calculation were based on the current reporting interval (25 February 2023 to 24 February 2024).

c: Seriousness and outcome have been presented for all events. A single case may report more than 1 event.

Of these 13 post-marketing cases reported as booster, the most frequently reported country/territory of origin (≥6) was Germany (n=10). These cases concerned 6 females, 6 males, and 1 did not report sex. The age range was from 21 to 77 years.

The frequency distribution of the MedDRA PTs reported in post-marketing cases reported as booster is presented in Table 25.

Table 25: Frequency Distribution of MedDRA PTs in Post-marketing Cases Reported as Booster and Reporting Concomitant Vaccination With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Interval Reporting interval[a]		Number of Events Reported Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
Injection site pain	0	11	0	53
Headache	0	9	4	43
Fatigue	0	7	2	47
Myalgia	0	6	1	22
Arthralgia	0	4	1	19
Malaise	0	4	1	22
COVID-19 immunisation	0	3	0	16
Dizziness	0	3	1	15
Back pain	0	2	1	7
Chills	0	2	1	16
Pyrexia	0	2	2	22

Table 25: Frequency Distribution of MedDRA PTs in Post-marketing Cases Reported as Booster and Reporting Concomitant Vaccination With the Use of Ad26.COV2.S

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

a: The MedDRA PTs with a frequency ≥2 have been presented. The MedDRA PTs are sorted by decreasing order for the current reporting interval (25 February 2023 to 24 February 2024). A single case may report more than 1 MedDRA PT.

b: For the cumulative column, the events were presented in decreasing order based on the event counts of the current reporting interval (25 February 2023 to 24 February 2024).

The most frequently (n≥5) reported events included injection site pain (n=11), headache (n=9), fatigue (n=7), and myalgia (n=6). The mean and median TTO were 193.2 days and 1 day, respectively, and the range was from same day to 921 days. Of the 83 events, 74 reported outcomes and are as follows: resolving (n=38), not resolved (n=18), resolved (n=16) and resolved with sequelae (n=2).

Of the 13 post-marketing cases reported as booster, 5 had the dates of concomitant vaccine administration specified, of which 2 documented coadministration on the same day as Ad26.COV2.S. Dates of vaccination were not specified for the remaining 8 cases. An overview of events in these cases is included in Table 26. Most of the events represent reactogenicity.

Table 26: Overview of MedDRA PTs in Post-marketing Cases Reported as Booster Reporting Concomitant Vaccinations With the Use of Ad26.COV2.S (Cases=13)

MedDRA PTs	Number of Events[a]
Cases Reporting Specified Dates of Concomitant Vaccine Administration (n=5)	
Fatigue	6
Injection site pain	4
Arthralgia	3
COVID-19 immunisation	3
Headache	3
Cases Reporting Unspecified Dates of Concomitant Vaccine Administration (n=8)	
Injection site pain	7
Headache	6
Myalgia	6
Malaise	4
Dizziness	2

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 ≥2 have been presented.

Literature ICSR

ICSR literature cases received during the current reporting interval were reviewed, and no information was identified that would change the information known about Use with concomitant vaccination.

Line Listings

Death: During the current reporting interval (25 February 2023 to 24 February 2024), no fatal case was retrieved.

Booster: A cumulative CIOMS II LL of cases reported as booster is presented in Appendix 7.2.

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 was observed. Based on review of all the available data, no safety concerns have been identified for use with concomitant vaccines during the reporting interval.

15.4. Vaccination Anxiety-related Reactions

In the Final Assessment Report (FAR), the PRAC Rapporteur for the Ad26.COV2.S PBRER dated 25 February 2022 to 24 August 2022, circulated on 14 April 2023 (PRAC AR 2023) (procedure number: EMEA/H/C/PSUSA/00010916/202208) indicated that,

"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".

This section will not be included within the body of this PBRER and future PBRERs; however, a separate subsection is found in Appendix 7.3 for those markets requiring this information.

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 core Risk Management Plan (cRMP) for Ad26.COV2.S based on past experiences in the development of vaccines against the 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 a specific vaccine-preventable disease in a person who is appropriately and fully vaccinated, 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 confirmation that the disease is specifically targeted by the vaccine (see Appendix 5).

Methods

The Company global safety database was searched for medically confirmed and medically unconfirmed cases received during this reporting interval and cumulatively, coded to the search criteria provided in Appendix 5.

For the purposes of this analysis, all medically confirmed cases with a TTO >14 days and reporting a Preferred Term (PT) consistent with a COVID-19 diagnosis (Asymptomatic COVID-19, Breakthrough COVID-19, Coronavirus infection, Coronavirus pneumonia, Coronavirus test positive, COVID-19, COVID-19 pneumonia, Loss of therapeutic response, Post-acute COVID19 syndrome, SARS-CoV-2 RNA increased, SARS-CoV-2 sepsis, SARS-CoV-2 test positive, SARS-CoV-2 viraemia, Vaccine derived SARS-CoV-2 infection, Vaccination failure [except cases where suspected COVID-19 PTs are also reported], and Virologic failure) or laboratory findings of positive polymerase chain reaction (PCR) test confirming COVID-19 positivity were considered as confirmed vaccination failures. Medically confirmed cases with a TTO >14 days and reporting the PT Suspected COVID-19 or a COVID-19 laboratory test PT with no result will be considered as suspected vaccination failures.

During the current reporting interval, it was noted that an increased number of cases were received that reported the PT of "COVID-19 immunisation" without other PTs indicative of vaccination failure/lack of efficacy/effectiveness. This EOI will no longer be considered in the analysis, thereby excluding any cases not reporting other EOIs for this topic.

Results/Discussion

Post-marketing Source Cases

Primary Dose

During this reporting interval, a total of 571 (509 medically confirmed and 62 medically unconfirmed) post-marketing, initial, primary-dose cases reporting events of vaccine failure or LOE were identified. There were 516 serious and 55 nonserious cases which reported a total of 595 EOIs (511 serious, 84 nonserious).

Cumulatively, 15,641 (13,063 medically confirmed and 2,578 medically unconfirmed) post-marketing, primary-dose cases reporting events of vaccine failure or LOE were identified. There were 13,778 serious and 1,863 nonserious cases which reported a total of 27,391 (24,359 serious and 3,032 nonserious)

An overview of these cases is presented in Table 27.

Table 27: Characteristics of Post-marketing Primary-dose Cases Involving the Use of Ad26.COV2.S and Reporting Vaccine Failure or Lack of Efficacy/Effectiveness

Case Characteristics		Number of Cases Received During the Interval Reporting Interval=571	Number of Cases Received Cumulatively=15,641[a]
Sex	Male	407	8,627
	Female	104	5,641
	NR	60	1,373
Age (Years)[b]	<18	0	28
Minimum: 18	18 to 35	274	6,489
Maximum: 89	36 to 50	93	4,267
Mean: 38	51 to 64	99	2,657
Median: 32	≥65	30	1,072
	Adult	7	61
	Neonate	3	17
	Infant	6	10
	Elderly	0	7
	Foetus	1	1
	Adolescent	0	1
	NR	58	1,031
Sources	Spontaneous	526	15,416
	Clinical study (noninterventional, solicited)	44	218
	Clinical study (noninterventional, unsolicited)	1	7
Country/Territory[c]	Portugal	432	1,078
	United States of America	69	2,247
	Germany	17	409
	Greece	20	92
	Romania	8	12
Event Characteristics		**Number of Events=595**	**Number of Events=27,391**
Seriousness Criteria (Event Level)[d]	Other medically important condition	461	22,651
	Hospitalisation	47	1,542
	Death	7	358
	Life-threatening	8	300
	Disability	5	92
	NR	84	3,032
Seriousness (Event Level)[d]	Serious	511	24,359
	Nonserious	84	3,032
Outcome (Event Level)[d]	Resolved	179	1,247
	Not resolved	20	806
	Resolving	91	600
	Fatal	7	358
	Resolved with sequelae	1	11
	NR	297	24,369

Table 27: Characteristics of Post-marketing Primary-dose Cases Involving the Use of Ad26.COV2.S and Reporting Vaccine Failure or Lack of Efficacy/Effectiveness

Key: NR=Not Reported

a: For the cumulative column, the counts were presented in decreasing order based on the current reporting interval (25 February 2023 to 24 February 2024).

b: The median and mean age calculation were based on the current reporting interval (25 February 2023 to 24 February 2024). Age at the time of Adverse Event is considered and Age group was presented for cases where age was not reported.

c: The countries reporting cases with frequency ≥5 are presented in the table.

d: Seriousness criteria, seriousness, and outcome have been presented for the events of interest. A single case may report more than 1 event and 1 event may report with more than 1 seriousness criteria.

Of these 571 cases received during the current interval, the most frequently reported countries/territories of origin (≥10) were Portugal (n=432), the US (n=69), Greece (n=20) and Germany (n=17). These cases concerned 407 males, 104 females, and 60 that did not report sex. The age range was from 18 to 89 years when reported.

The frequency distribution of the MedDRA PTs of interest reported is presented in Table 28.

Table 28: Frequency Distribution of MedDRA PTs in Post-marketing Primary-dose Cases Reporting Vaccine Failure or Lack of Efficacy/Effectiveness With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Received During the Interval Reporting Interval[a]		Number of Events Received Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
Drug ineffective	286	1	475	4
Vaccination failure	164	0	12,224	0
COVID-19	30	38	10,497	1,055
Suspected COVID-19	8	35	146	702
SARS-CoV-2 test positive	5	4	257	1,158
Thrombosis with thrombocytopenia syndrome	7	0	106	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

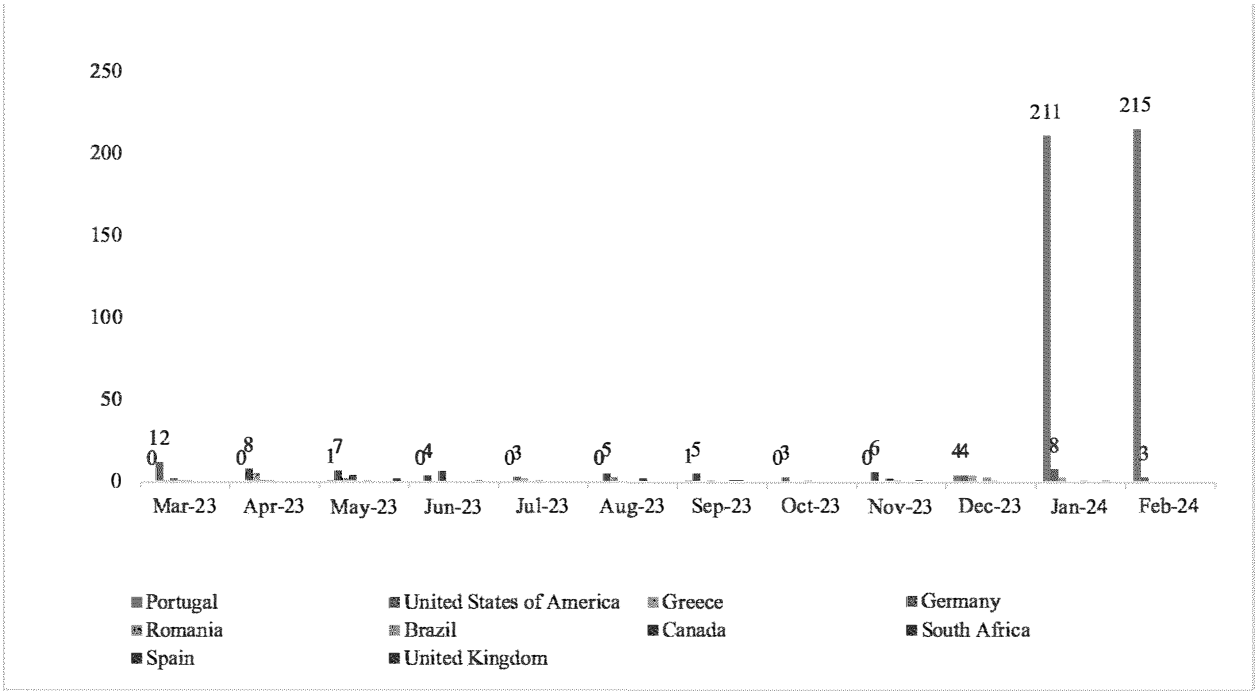
a: The MedDRA PTs of interest with a frequency ≥5 have been presented and sorted by decreasing order for the reporting interval (25 February 2023 to 24 February 2024). A single case may report more than 1 MedDRA PT.

b: For the cumulative column, the counts were presented in decreasing order based on the current reporting interval (25 February 2023 to 24 February 2024).

During the reporting interval, the EOIs (≥5) included drug ineffective (n=287), vaccination failure (n=164), COVID-19 (n=68), suspected COVID-19 (n=43), SARS-CoV-2 test positive (n=9) and thrombosis with thrombocytopenia syndrome (n=7). The mean and median TTO were 85 days and 39 days, respectively, and the range was from 0 to 1,064 days. Of the 595 EOIs, outcomes were reported for 298 as follows: resolved (n=179), resolving (n=91), not resolved (n=20), fatal (n=7), and resolved with sequelae (n=1).

Figure 3 depicts primary-dose cases reporting vaccine failure or lack of efficacy/effectiveness involving the use of Ad26.COV2.S from the top 10 countries/territories by month.

Figure 3: Post-marketing Primary-dose Cases Reporting Vaccine Failure or Lack of Efficacy/Effectiveness With the Use of Ad26.COV2.S From the Top 10 Countries/Territories by Month (Interval: 25 February 2023 to 24 February 2024).



Please see the Discussion section below for observations from Figure 3.

The TTO reported in these 571 cases is presented in Table 29.

Table 29: Time to Onset in Post-marketing Primary-dose Cases Reporting Vaccine Failure or Lack of Efficacy/Effectiveness With the Use of Ad26.COV2.S (Cases=571)

TTO	Number of Cases[a]
≤14 days	88
>14 days but ≤28 days	81
>28 days	283
NR	119
Total	**571**

Key: NR=Not Reported; TTO=Time to Onset

a: One case may report more than 1 event and hence more than 1 latency. In 15 cases, we have fetal exposure during pregnancy.

Of the total 571 cases received during the interval, 165 medically confirmed reported a TTO >14 days and reported PTs consistent with a COVID-19 diagnosis or laboratory finding of positive PCR test confirming COVID-19 positivity. One of the medically confirmed cases with a TTO >14 days reported the PT suspected COVID-19 or a COVID-19 laboratory test PT with no result. Cases and events of confirmed vaccination failure (n=165) and suspected vaccination failure (n=1) are described in Table 30.

Table 30: Events of Confirmed Vaccination Failure in Post-marketing Primary-dose Cases Involving the Use of Ad26.COV2.S (Cases=166; Events=174)

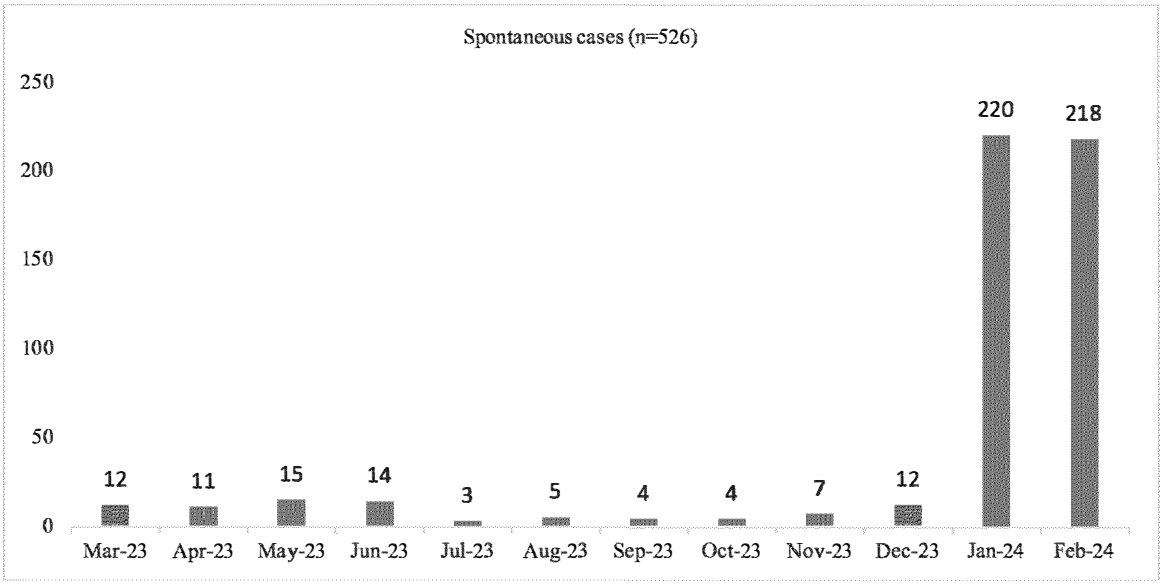
Confirmed Vaccination Failure (Cases=165)	
Preferred Term	**Number of Events**
Vaccination failure	139
COVID-19	13
SARS-CoV-2 test positive	5
COVID-19 pneumonia	1
Total confirmed COVID-19 events	**173[a]**
Suspected Vaccination Failure (Cases=1)	
Suspected COVID-19	**1**
Subtotal	**1**
Total	**174**

Key: COVID-19=Coronavirus Disease-2019; EOI=Event(s) of Interest; SARS-CoV-2=Severe Acute Respiratory Syndrome Coronavirus 2

a: In addition to events presented above, 15 confirmed cases reported the MedDRA PT Drug ineffective; this event is not presented in the table.

Figure 4 depicts the case count of primary-dose spontaneous cases by month involving the use of Ad26.COV2.S and reporting vaccine failure or lack of efficacy/effectiveness from 25 February 2023 to 24 February 2024.

Figure 4: Case Count of Post-marketing Primary-dose Spontaneous Cases by Month Reporting Vaccine Failure or Lack of Efficacy/Effectiveness With the Use of Ad26.COV2.S (Interval: 25 February 2023 to 24 February 2024).



Please see the Discussion section below for observations from Figure 2.

The events are further sorted by seriousness and their respective outcomes in Table 31 and Table 32.

Table 31: Serious MedDRA PTs and Their Outcomes in Post-marketing Primary-dose Cases Reporting Vaccine Failure or Lack of Efficacy/Effectiveness With the Use of Ad26.COV2.S (Events=511)

MedDRA PTs	Number of Event Outcomes					
	Fatal	Not Resolved	Resolved	Resolving	NR	Total Number of Events[a]
Drug ineffective	0	6	135	66	79	286
Vaccination failure	0	4	24	18	118	164
COVID-19	5	3	4	1	17	30
Suspected COVID-19	0	0	1	0	7	8
Thrombosis with thrombocytopenia syndrome[b]	1	2	0	0	4	7
SARS-CoV-2 test positive	1	0	1	0	3	5
COVID-19 pneumonia	0	1	0	1	2	4
Therapy non-responder	0	0	0	0	4	4

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 MedDRA PT. The serious EOI having frequency ≥4 have been presented.

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

Table 32: Nonserious MedDRA PTs and Their Outcomes in Post-marketing Primary-dose Cases Reporting Vaccine Failure or Lack of Efficacy/Effectiveness With the Use of Ad26.COV2.S (Events=84)

MedDRA PTs	Number of Event Outcomes					
	Not Resolved	Resolved	Resolved With Sequelae	Resolving	NR	Total Number of Events[a]
COVID-19	3	10	0	2	23	38
Suspected COVID-19	1	3	0	2	29	35
SARS-CoV-2 test positive	0	0	0	0	4	4
Breakthrough COVID-19	0	1	1	0	0	2
Post-acute COVID-19 syndrome	0	0	0	1	1	2

Key: COVID-19=Coronavirus Disease-2019; EOI=Event(s) of Interest; 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 MedDRA PT. The serious EOI having frequency ≥2 have been presented.

Booster Dose

During this reporting interval, a total of 111 (33 medically confirmed and 78 medically unconfirmed) post-marketing, initial cases reported as booster were identified. There were 65 serious and 46 nonserious cases which reported a total of 159 EOIs (75 serious, 84 nonserious). Of these cases, 92 were heterologous and 19 were homologous.

Cumulatively, 997 (333 medically confirmed and 664 medically unconfirmed) cases reported as booster were identified. There were 560 serious and 437 nonserious cases which reported a total of 1,435 EOIs (642 serious, 793 nonserious). Of these cases, 631 were heterologous and 366 were homologous.

An overview of these cases reporting booster dose is presented in Table 33.

Table 33: Characteristics of Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Vaccine Failure or Lack of Efficacy/Effectiveness

Case Characteristics		Number of Cases Received During the Interval Reporting Interval=111	Number of Cases Received Cumulatively=997[a]
Sex	Female	36	431
	Male	36	338
	NR	39	228
Age (Years)[b]	18 to 35	6	149
Minimum: 24	36 to 50	11	205
Maximum: 80	51 to 64	27	229
Mean: 55.7	≥65	14	156
Median: 58.5	Infant	1	2
	Adult	1	8
	Elderly	1	7
	NR	50	241
Sources	Spontaneous	97	887
	Clinical study (noninterventional, solicited)	14	85
	Clinical study (noninterventional, unsolicited)	0	25
Country/Territory[c]	United States	69	601
	Germany	14	49
	Canada	7	56
	Greece	6	16
	Brazil	4	76
	Austria	2	40
	Spain	2	12
Event Characteristics		**Number of Events=159**	**Number of Events=1,435**
Seriousness Criteria (Event Level)[d]	Other medically important condition	63	536
	Hospitalisation	13	98
	Death	4	21
	Life-threatening	2	12
	Disability	0	4
	Nonserious	84	1
	NR	1	793

Table 33: Characteristics of Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Vaccine Failure or Lack of Efficacy/Effectiveness

Case Characteristics		Number of Cases Received During the Interval Reporting Interval=111	Number of Cases Received Cumulatively=997[a]
Seriousness (Event Level)[d]	Serious	75	642
	Nonserious	84	793
Outcome (Event Level)[d]	Not resolved	28	211
	Resolving	24	139
	Resolved	15	172
	Fatal	4	21
	Resolved with sequelae	3	4
	NR	85	888

Key: NR=Not Reported

a: For the cumulative column, the counts were presented in decreasing order based on the current reporting interval (25 February 2023 to 24 February 2024).

b: The median and mean age calculations were based on the current reporting interval (25 February 2023 to 24 February 2024). Age group was presented for cases where age was not reported.

c: Countries/territories with frequency ≥2 were presented in decreasing order for the current reporting interval.

d: Seriousness criteria, seriousness and outcome have been presented for the events. A single case may report more than 1 event and 1 event may report more than 1 seriousness criteria.

Of these 111 cases reported as booster, the most frequently reported countries/territories of origin (≥7) were the US (n=69), Germany (n=14) and Canada (n=7). These cases concerned 36 females, 36 males, and 39 that did not report sex. The age range was from 24 to 80 years when reported.

The frequency distribution of the MedDRA PTs in cases reported as booster is presented in Table 34.

Table 34: Frequency Distribution of MedDRA PTs in Post-marketing Cases Reported as Booster and Reporting Vaccine Failure or Lack of Efficacy/Effectiveness

MedDRA PTs	Number of Events Received During the Interval Reporting Interval[a]		Number of Events Received Cumulatively[b]	
	Nonserious	Serious	Nonserious	Serious
COVID-19	44	16	406	113
Suspected COVID-19	33	6	246	29
Vaccination failure	0	33	1	391
Drug ineffective	0	14	1	42
Post-acute COVID-19 syndrome	2	1	6	1
SARS-CoV-2 test positive	2	1	116	14
Breakthrough COVID-19	1	1	3	1
COVID-19 pneumonia	0	2	0	18

Table 34: Frequency Distribution of MedDRA PTs in Post-marketing Cases Reported as Booster and Reporting Vaccine Failure or Lack of Efficacy/Effectiveness

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

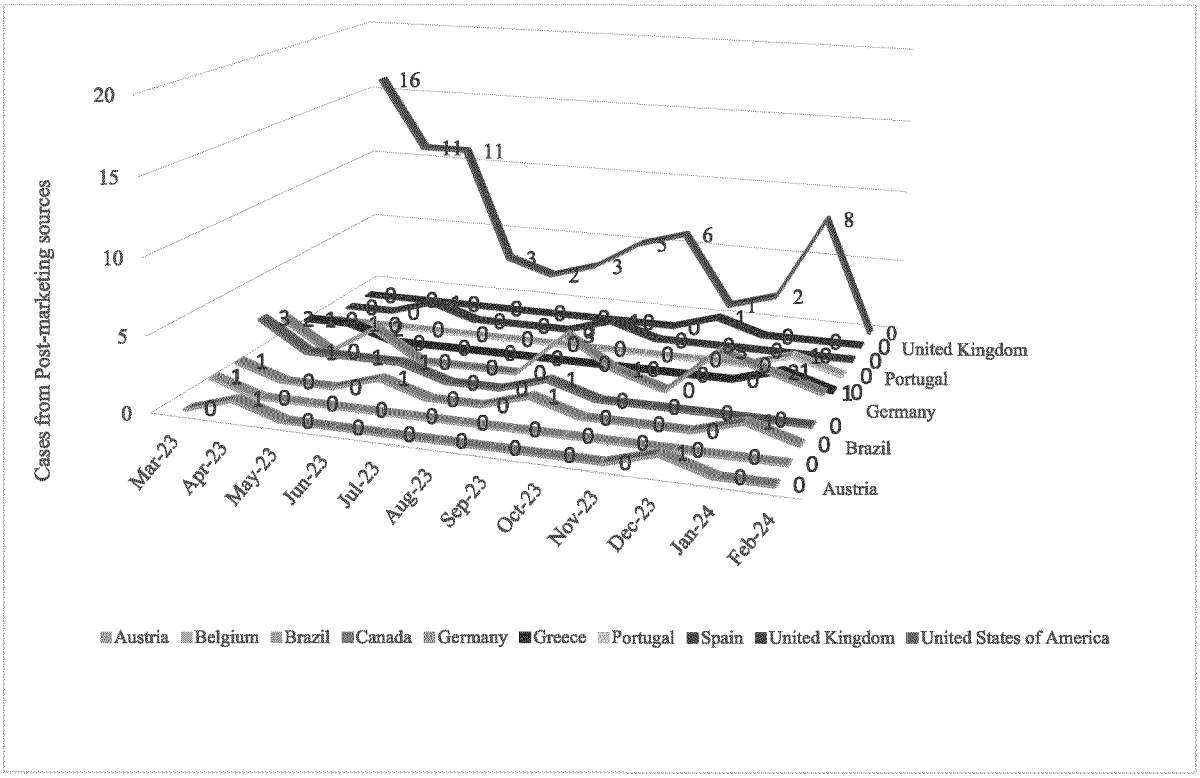
a: The MedDRA PTs of interest with a frequency ≥2 have been presented and are sorted by decreasing order for the current reporting interval (25 February 2023 to 24 February 2024). A single case may report more than 1 MedDRA PT.

b: For the cumulative column, the counts were presented in decreasing order based on the current reporting interval (25 February 2023 to 24 February 2024).

The EOIs (≥2) included COVID-19 (n=60), suspected COVID-19 (n=39), vaccination failure (n=33), drug ineffective (n=14), post-acute COVID-19 syndrome, SARS-CoV-2 test positive (n=3 each), COVID-19 pneumonia and breakthrough COVID-19 (n=2 each). The mean and median TTO were 550.2 and 632 days, respectively, and the range was from 0 to 1,133 days. Of the 159 EOIs, outcomes were reported for 74 as follows: not resolved (n=28), resolving (n=24), resolved (n=15), fatal (n=4), and resolved with sequelae (n=3).

Figure 5 below depicts the cases reported as booster from the top 10 countries/territories by month.

Figure 5: Post-marketing Cases Reported as Booster and Reporting Vaccine Failure or Lack of Efficacy/Effectiveness With the Use of Ad26.COV2.S From the Top 10 Countries/Territories by Month (Interval: 25 February 2023 to 24 February 2024).



The TTO reported for the 111 cases is presented in Table 35.

Table 35: Time to Onset in Post-marketing Cases Reported as Booster and Reporting Vaccine Failure or Lack of Efficacy/Effectiveness (Cases=111)

TTO	Number of Cases[a]
≤14 days	2
>14 days but ≤28 days	0
>28 days	61
NR	48

Key: NR=Not Reported; TTO=Time to Onset
a: One case may report more than 1 event and hence more than 1 latency.

Of the total 111 cases reported as booster received during interval, 11 medically confirmed reported a TTO >14 days and reported PTs consistent with a COVID-19 diagnosis or laboratory finding of positive PCR test confirming COVID-19 positivity.

Cases and events of confirmed vaccination failure (n=11) and suspected vaccination failure (n=3) with booster doses are described in Table 36.

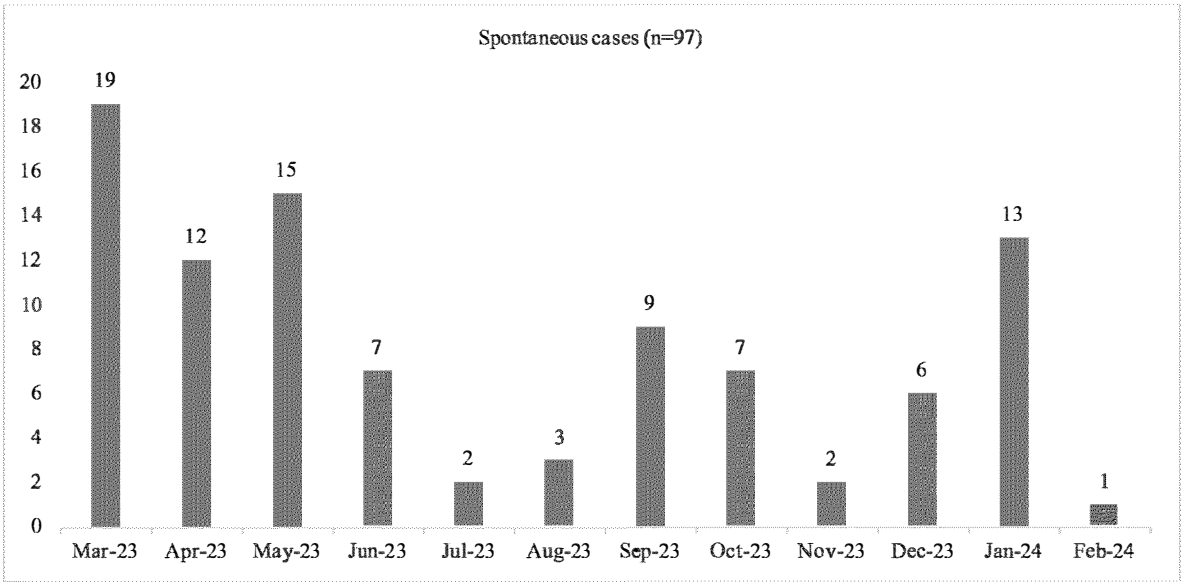
Table 36: Events of Confirmed and Suspected Vaccination Failure in Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S (Cases=14; Events=17)

Confirmed Vaccination Failure (Cases=51)	
Preferred Term	**Number of Events**
COVID-19	9
Vaccination failure	2
COVID-19 pneumonia	2
SARS-CoV-2 test positive	1
Total confirmed COVID-19 events	**14**
Suspected Vaccination Failure (Cases=3)	
Suspected COVID-19	3
Total suspected COVID-19 events	**3**
Grand Total	***17***

Key: COVID-19=Coronavirus Disease-2019; SARS-CoV-2=Severe Acute Respiratory Syndrome Coronavirus 2

Figure 6 depicts the monthly case count of spontaneous cases reported as booster from 25 February 2023 to 24 February 2024.

Figure 6: Case Count of Post-marketing Spontaneous Cases Reported as Booster Reporting Vaccine Failure or Lack of Efficacy/Effectiveness With the Use of Ad26.COV2.S (Interval: 25 February 2023 to 24 February 2024).



The EOIs are further sorted by seriousness and their respective outcomes in Table 37 and Table 38.

Table 37: Serious MedDRA PTs and Their Outcomes in Cases Reported as Booster Reporting Vaccine Failure or Lack of Efficacy/Effectiveness With the Use of Ad26.COV2.S (Events=75)

MedDRA PTs	Number of Event Outcomes						
	Fatal	Not Resolved	Resolved	Resolved With sSquelae	Resolving	NR	Total Number of Events[a]
Vaccination failure	1	0	1	0	1	30	33
COVID-19	1	1	3	0	1	10	16
Drug ineffective	0	0	2	1	0	11	14
Suspected COVID-19	0	0	0	1	1	4	6
COVID-19 pneumonia	1	0	1	0	0	0	2

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 MedDRA PT. The serious events with frequency ≥2 have been presented.

Table 38: Nonserious MedDRA PTs of Interest and Their Outcomes in Cases Reported as Booster Reporting Vaccine Failure or Lack of Efficacy/Effectiveness With the Use of Ad26.COV2.S (Events=84)

MedDRA PTs	Number of Event Outcomes				
	Not Resolved	Resolved	Resolving	NR	Total Number of Events
COVID-19	16	5	11	12	44
Suspected COVID-19	10	0	10	13	33
Post-acute COVID-19 syndrome	1	0	0	1	2
SARS-CoV-2 test positive	0	2	0	0	2
Breakthrough COVID-19	0	0	0	1	1
Therapeutic product effect decreased	0	0	0	1	1
Therapeutic response decreased	0	1	0	0	1

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

Janssen-sponsored and Janssen-supported Clinical Study Cases

Information on Janssen-sponsored and Janssen-supported clinical study cases can be found in Section 13, Lack of Efficacy in Controlled Clinical Trials, and Section 17, Benefit Evaluation, of the PBRER.

Literature ICSR

Fifty-seven ICSR literature cases received during the current reporting interval were reviewed, and no information was identified that would change the information known about vaccine failure or lack of efficacy/effectiveness.

Line Listings

Death: During the current reporting interval (25 February 2023 to 24 February 2024), a total of 8 fatal cases were retrieved. Of these cases, 11 reported a fatal EOI.

A CIOMS II LL of the fatal cases is presented in Appendix 7.4.1. Additional information on the fatal cases can also be found in Appendix 7.26, Death.

Booster: A cumulative CIOMS II LL of cases reported as booster is presented in Appendix 7.4.2.

Discussion

For the current reporting interval of 25 February 2023 to 24 February 2024, a total of 180 cases meeting the criteria for confirmed or suspected vaccination failure were reported, which is notably less than the number of cases identified for the previous PBRER interval of 25 August 2022 to 24 February 2023 (n=1,046). This decrease in number is due to the overall decrease in reporting of vaccination failure/lack of efficacy cases in the current reporting interval (total 682 cases)

compared to the previous reporting interval (total of 1,415 cases) which in turn may be due to the lower exposure to the vaccine compared to last reporting interval.

In the current reporting interval, the country with the highest number of cases was Portugal, accounting for 75.6% of primary dose cases reported. Most of these cases were received in the month of January 2024 and February 2024. This spike resulted due to bulk reporting of cases by Health Authority, as most cases (431/432, 99.8%) were received from Health authority (mostly EVHUMAN) with minimal case details ie, no medical history, concomitant medications and clinical course in the majority of cases, and not necessarily occurring within date of reporting to the Company. None reported events that were fatal, life-threatening, required hospitalisation, or were disabling. Compared to the previous interval (n=150), a decrease was observed for vaccination failure cases following the booster dose in the US (n=69).

In total 8 cases from the current interval reported a fatal outcome (6 primary dose and 2 booster cases). Of these 8 cases, 3 were assessed as confirmed LOE (1 primary dose, a 2 booster cases). The primary dose case involved an 82-year-old male with underlying multiple myeloma (on chemotherapy) and diabetes mellitus which could be confounding to the fatal outcome. It was reported that after a latency of 515 days, the patient died from various events including cerebrovascular accident and COVID-19. It was unknown if autopsy was performed. The first booster case involved a 66-year-old female with concurrent Sjoegren's syndrome, rheumatoid arthritis, capilar angioma, and anxiodepressive syndrome. It was reported that the patient died from COVID-19 pneumonia, and nosocomial pneumonia. It's notable that Ad26.COV2.S was administered 404 days before the onset of events, and the patients booster dose was with non-company vaccine tozinameran 110 days before the onset of events. It was unknown if an autopsy was performed. The second booster dose case reported a 60-year-old male with concurrent bipolar disorder, hypertension, and reflux hypothyroidism. The patient received primary dose with Ad26.COV2.S on an unspecified date, with no adverse events were observed following vaccination with first dose. The patient received booster dose with Ad26.COV2.S and 414 days later presented with shortness of breath, discoloration, body aches, headache and chest pain. Findings were compatible with bronchitis and superimposed bronchiolitis, as well as multi-vessel coronary calcifications. The patient had a positive SARS-CoV-2 test. The patients status deteriorated with reported encephalopathy and clots in the urethra. The patient passed away 425 days after administration of last dose of Ad26.COV2.S. It was unknown if autopsy was performed or not.

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 interval 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 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

Post-marketing Sources (Including Spontaneous and Solicited) Cases

Primary Dose

During the reporting interval, a total of 24 (6 medically confirmed and 18 medically unconfirmed) post-marketing, primary dose cases reporting serious AEs of reactogenicity were identified. These 24 cases reported a total of 52 serious EOIs.

An overview of these cases is presented in Table 39.

Table 39: 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 Reporting Interval=24	Number of Cases Received Cumulatively=1,499[a]
Sex	Female	13	807
	Male	11	675
Age (Years)[b]	18 to 35	8	455
Minimum: 18	36 to 50	4	486
Maximum: 71	51 to 64	9	356
Mean: 44.5	≥65	1	170
Median: 46.5	Adult	2	6

Table 39: 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 Reporting Interval=24	Number of Cases Received Cumulatively=1,499[a]
Source	Spontaneous	23	1,442
	Clinical study (noninterventional; solicited)	1	57
Country/Territory	Germany	13	305
	United States	3	476
	Spain	2	11
	Austria	2	36
	Greece	1	36
	Korea, Republic of	1	105
	Romania	1	79
	South Africa	1	64
Event Characteristics		**Number of Events=52**	**Number of Events=3,584**
Seriousness (Event Level)[c]	Serious	52	3,584
Outcome (Event Level)[c]	Not resolved	19	1,290
	Resolved with sequelae	11	113
	Resolved	5	709
	Resolving	3	750
	NR	14	652

Key: EOI=Event(s) of Interest; NR=Not Reported

a: For the cumulative column, the counts were presented in decreasing order based on the current reporting interval (25 February 2023 to 24 February 2024).

b: The median and mean age calculations were based on the current reporting interval (25 February 2023 to 24 February 2024). Cases where the age was not reported, the age group has been presented.

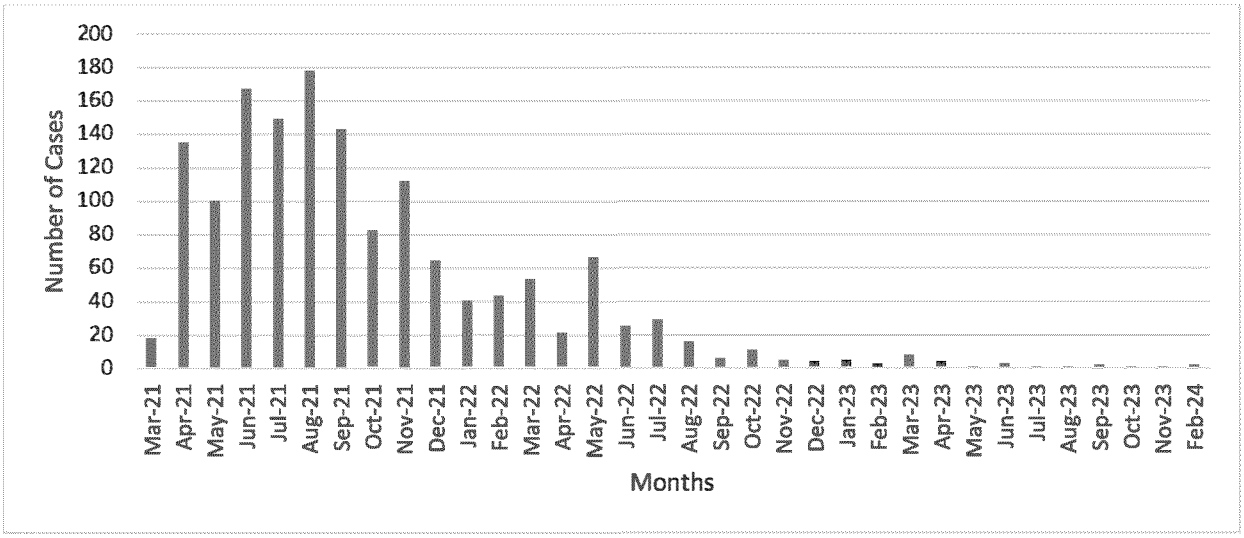
c: Seriousness and outcome have been presented for the EOI. A single case may report more than 1 EOI.

Of these 24 cases received, the reported countries/territories of origin were Germany (n=13); the US (n=3); Austria and Spain (n=2 each); and Greece, Korea, Republic of, Romania, and South Africa (n=1 each). The cases concerned 13 females and 11 males. The age range was from 18 to 71 years.

Cumulatively, 1,499 (672 medically confirmed and 827 medically unconfirmed) primary dose cases reporting reactogenicity were identified.

Figure 7 presents the number of cases received cumulatively by month (n=1,499).

Figure 7: Cumulative Case Reports by Month



Booster Dose

During the reporting interval, no initial cases reported as booster were identified.

Cumulatively, 47 (15 medically confirmed and 32 medically unconfirmed) post-marketing cases reported as booster were identified.

Local Reactogenicity Reactions

Primary Dose

Four post-marketing primary dose cases reported local reactogenicity reactions. The reported countries/territories of origin were Germany, Korea, Republic of, South Africa, and the US (n=1 each). These cases concerned 1 male and 3 females. The age range was from 46 to 61 years.

Cumulatively, 144 (48 medically confirmed and 96 medically unconfirmed) post-marketing primary dose cases reported local reactogenicity reactions. The frequency distribution of MedDRA PTs reflecting potential local reactions is presented in Table 40. The event outcomes are presented in Table 41.

Table 40: Frequency of MedDRA PTs of Interest in Post-marketing Primary Dose Cases Reporting Potential Local Reactogenicity Reactions With the Use of Ad26.COV2.S

MedDRA PTs	Number of Serious Events Received During the Reporting Interval[a]	Number of Serious Events Received Cumulatively[b]
Injection site pain	3	128
Injection site erythema	1	11
Injection site swelling	1	29
Vaccination site pain	1	20

Table 40: Frequency of MedDRA PTs of Interest in Post-marketing Primary Dose Cases Reporting Potential Local Reactogenicity Reactions With the Use of Ad26.COV2.S

Key: EOI=Event(s) of Interest; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term

a: The MedDRA PTs of interest were sorted by decreasing order for the reporting interval (25 February 2023 to 24 February 2024). A single case may report more than 1 EOI.

b: For the cumulative column, the counts were presented in the decreasing order based on the current reporting interval (25 February 2023 to 24 February 24).

Table 41: Frequency Distribution of MedDRA PTs of Interest in Post-marketing Primary Dose Cases and Outcomes Reporting Potential Local Reactogenicity Reactions With the Use of Ad26.CoV2.S

MedDRA PTs	Number of Event Outcomes				
	Not Resolved	Resolved	Resolved With Sequelae	NR	Total Number of Serious Events
Injection site pain	1	1	0	1	3
Injection site erythema	0	0	0	1	1
Injection site swelling	0	0	0	1	1
Vaccination site pain	0	0	1	0	1
Total	**1**	**1**	**1**	**3**	**6**

Key: MedDRA=Medical Dictionary for Regulatory Activities; NR=Not Reported; PT=Preferred Term

The reported EOIs were injection site pain (n=3) and injection site erythema, injection site swelling, and vaccination site pain (n=1 each). The mean and median TTO were 1.5 and 2 days, respectively, and the range was from 0 to 3 days. Of the 6 EOIs, outcomes were reported for 3 and are as follows: not resolved, resolved, and resolved with sequelae (n=1 each).

Additionally, cases were reviewed to determine if there were any serious important identified risk (eg, TTS or Thrombocytopenia, including immune thrombocytopenia) events reported. Of these 4 cases, TTS (n=1) was reported. This case is discussed in Section 16.3.1.1, Thrombosis With Thrombocytopenia Syndrome.

Booster Dose

There were no post-marketing, initial booster cases which reported local reactogenicity reactions.

Cumulatively, 4 medically unconfirmed post-marketing booster cases reported local reactogenicity reactions.

Additionally, cases were reviewed to determine if there were any serious important identified risks (eg, TTS or Thrombocytopenia, including immune thrombocytopenia) events reported. There were no post-marketing, initial booster cases retrieved to determine if there were any serious important identified risk events reported.

Systemic Reactogenicity Reactions

Primary Dose

Twenty-three post-marketing primary dose cases reported systemic reactogenicity reactions. The most frequently reported countries/territories of origin were Germany (n=13); Austria, Spain, and the US (n=2 each); Greece, Korea, Republic of, Romania, and South Africa (n=1 each). These cases concerned 12 females and 11 males. The age range was from 18 to 71 years.

Cumulatively, 1,474 (657 medically confirmed and 817 medically unconfirmed) post-marketing primary dose cases reported systemic reactogenicity reactions. The frequency distribution of MedDRA PTs reflecting potential systemic reactions is presented in Table 42. The event outcomes are presented in Table 43.

Table 42: Frequency of MedDRA PTs of Interest in Post-marketing Primary Dose Cases Reporting Potential Systemic Reactogenicity Reactions With the Use of Ad26.COV2.S

MedDRA PTs	Number of Serious Events Received During the Reporting Interval[a]	Number of Serious Events Received Cumulatively[b]
Fatigue	11	384
Dizziness	7	382
Myalgia	7	247
Asthenia	4	158
Headache	4	585
Vomiting	3	137
Chills	2	245
Hypoaesthesia	2	158
Pyrexia	2	425

Key: EOI=Event(s) of Interest; 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 the decreasing order for the reporting interval (25 February 2023 to 24 February 2024). A single case may report more than 1 EOI.

b: For the cumulative column, the counts were presented in the decreasing order based on the current reporting interval (25 February 2023 to 24 February 2024).

Table 43: Frequency Distribution of MedDRA PTs of Interest in Post-marketing Primary Dose Cases and Outcomes Reporting Potential Systemic Reactogenicity Reactions With the Use of Ad26.CoV2.S

MedDRA PTs	Number of Event Outcomes					
	Not Resolved	Resolved	Resolved With Sequelae	Resolving	NR	Total Number of Serious Events
Fatigue	5	0	5	0	1	11
Dizziness	2	1	0	1	3	7
Myalgia	3	0	1	0	3	7
Asthenia	1	0	3	0	0	4
Headache	3	1	0	0	0	4
Vomiting	1	1	0	0	1	3
Pyrexia	0	0	0	1	1	2

Table 43: Frequency Distribution of MedDRA PTs of Interest in Post-marketing Primary Dose Cases and Outcomes Reporting Potential Systemic Reactogenicity Reactions With the Use of Ad26.CoV2.S

MedDRA PTs	Number of Event Outcomes					
	Not Resolved	Resolved	Resolved With Sequelae	Resolving	NR	Total Number of Serious Events
Hypoaesthesia	1	0	1	0	0	2
Chills	0	0	0	1	1	2
Diarrhoea	0	0	0	0	1	1
Arthralgia	1	0	0	0	0	1
Pain in extremity	0	1	0	0	0	1
Paraesthesia	1	0	0	0	0	1
Grand Total	**18**	4	**10**	**3**	**11**	**46**

Key: MedDRA=Medical Dictionary for Regulatory Activities; NR=Not Reported; PT=Preferred Term

The reported EOIs (n≥2) were fatigue (n=11); dizziness and myalgia (n=7); asthenia and headache (n=4 each); vomiting (n=3); and chills, hypoaesthesia, and pyrexia (n=2 each). The mean and median TTO were 1.4 days and 0 day, respectively, and the range was from 0 to 7 days. Of the 46 EOIs, outcomes were reported for 35 and are as follows: not resolved (n=18), resolved with sequelae (n=10), resolved (n=4), and resolving (n=3).

Additionally, cases were reviewed to determine if there were any reported important identified (eg, TTS or Thrombocytopenia, including immune thrombocytopenia). Of these 23 cases, TTS (n=3), and GBS (n=2) were reported. These cases are discussed in Section 16.3.1.1, Thrombosis With Thrombocytopenia Syndrome and Section 16.3.1.2, Guillain-Barré Syndrome respectively.

Booster Dose

During the reporting interval, there were no booster cases reporting systemic reactogenicity reactions.

Cumulatively, 47 (15 medically confirmed and 32 medically unconfirmed) post-marketing booster cases reported systemic reactogenicity reactions.

Additionally, cases were reviewed to determine if there were any reported important identified (eg, TTS or Thrombocytopenia, including immune thrombocytopenia) risk events. There were no post-marketing, initial booster cases retrieved to determine if there were any serious important identified risk events reported.

Clinical Trial Cases

During this reporting interval, 2 primary dose cases reporting local reactogenicity reactions were retrieved from a Janssen-supported Clinical Study (VAC31518COV3021). Both cases were received from South Africa and concerned a [redacted]-year-old female and a [redacted]-year-old female, respectively. The EOIs reported in these 2 cases were injection site pain and injection site reaction.

In both the cases, TTO was reported as 1 day, and the outcome for both events was reported as resolved.

Literature ICSR

No ICSR literature cases were received during the reporting interval.

Line Listings

Death: During the current reporting interval (25 February 2023 to 24 February 2024), no fatal cases reporting fatal events of reactogenicity were retrieved.

Booster: A cumulative CIOMS II LL of cases reported as booster is presented in Appendix 7.5.

Conclusion

The reported local and systemic reactogenicity reactions are in line with what is already included in the product information as common adverse reactions. The review of the cases received during the reporting interval have not shown any changes in terms of severity or outcome warranting changes to the prescribing information (PI).

16. SIGNAL AND RISK EVALUATION

16.1. Summary of Safety Concerns

16.1.1. At the Beginning of the Reporting Interval

The summary of safety concerns (ie, important identified risks, important potential risks, and missing information) at the beginning of the reporting interval to be included in the Ad26.COV2.S PBRER are based on cRMP (version 6.0, dated 25 October 2022) and are summarised in Table 44.

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 5.3 (dated 13 February 2023)
- 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 44: Important Identified Risks, Important Potential Risks, and Missing Information at the Beginning of the Reporting interval

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

a: Immune thrombocytopenia is characterised in the European Union Risk Management Plan, version 5.3, as an important identified risk "Thrombocytopenia, including immune thrombocytopenia."

16.1.2. At the End of the Reporting Interval

During the reporting interval, the safety concerns were re-evaluated as follows:

- The cRMP version 6.0 was updated to version 7.0 on 10 May 2023 with the addition of the important identified risk of "Myocarditis and pericarditis".
- The cRMP version 7.0 was updated to version 8.0 on 06 February 2024 with the removal of the missing information "Interaction with other vaccines" and reclassification of the important potential risk "Immune thrombocytopenia" to an important identified risk with renaming to "Thrombocytopenia, including immune thrombocytopenia."
- The EU-RMP version 5.3 was updated to version 7.1 on 13 June 2023.

These updates are discussed under appropriate subsections below including Section 16.3.

The updated summary of safety concerns is presented in Table 45.

Table 45: Important Identified Risks, Important Potential Risks, and Missing Information at the End of the Reporting Interval

Important Identified Risks	Thrombosis with thrombocytopenia syndrome Guillain-Barré syndrome Venous thromboembolism Myocarditis and pericarditis Thrombocytopenia, including immune thrombocytopenia
Important Potential Risks	Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD)
Missing Information	Use during pregnancy Use in breastfeeding women Use in immunocompromised patients Use in patients with autoimmune or inflammatory disorders Interaction with other vaccines[a] Use in frail patients with comorbidities (eg, chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders) Long-term safety

Table 45: Important Identified Risks, Important Potential Risks, and Missing Information at the End of the Reporting Interval

Key: EU-RMP=European Union Risk Management Plan
a: EU-RMP only

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 interval, the following signals were closed but with continued routine pharmacovigilance or closely monitored and discussed in future PBRERs/PSURs (see Appendix 3).

16.2.1.1.1. Cerebral Haemorrhage

Request: On 12 December 2022, a signal was identified based on a single case review for cerebral haemorrhage with the use of JCOVDEN® (Ad26.COV2.S). This topic has been reviewed by the Company in the past on 22 October 2020. New information has been received that warrants a new review of this topic. This signal was reassessed due to the association of events with fatal outcomes/serious medical consequences, the association with permanent disability/sequelae, the impact of the events on patient quality of life, the potential of the event to alter the benefit-risk profile, and the fact that is a safety topic with regulatory interest. This signal is also an unlisted event, due to the fact that this is a preventable event, due to the significant case volume, based on the statistical association between the drug and the event, and based on the temporal association of the events. The validation method included an interval case series review of relevant data in the Company global safety database from 25 February 2022 through 24 August 2022.

MAH Conclusion: Based on this review, there was insufficient evidence to suggest a reasonable possibility that cerebral haemorrhage is causally associated with Ad26.COV2.S vaccine. Key factors supporting this conclusion include:

- no imbalance in reporting rate of SMQ "Haemorrhagic CNS vascular conditions" was observed during the double-blind phase of the primary pooled analysis
- insufficient evidence regarding the causal role of the Ad26.COV2.S vaccine and cerebral haemorrhage based on the review of post-marketing data

- RWE Rapid Cycle analysis indicated lack of evidence of increased risk of cerebral haemorrhage with Ad26.COV2.S
- although different Mechanism Of Action (MOA) were proposed in the literature, no MOA has been identified yet for the development of cerebral haemorrhage in association with adenoviral vector COVID-19 vaccines

Three out of 4 databases used in the data mining analysis reported disproportionately for cerebral haemorrhage. The restricted haemorrhagic stroke O/E sensitivity analysis for the 1 to 28 days risk window (the established risk window for haemorrhagic stroke) also revealed statistically significant O/E ratios >1 for nearly all female and male age groups for the US and for female 18 to 29 years and 40 to 49 years age groups and male 18 to 29 years and 30 to 39 years age groups for the EU. However, although some imbalances are reported, further detailed review of the post-marketing data used in these analyses showed that the cases occurred outside the risk window, were confounded, or did not provide enough information to make a meaningful medical assessment.

Additional information on the analysis can be found is in Appendix 7.6.

16.2.1.1.2. Heavy Menstrual Bleeding

Request: On 12 December 2022 a signal was identified for Cerebral haemorrhage, with the use of Ad26.COV2.S following routine individual case assessment. On 17 January 2023 a signal was identified for the event Heavy menstrual bleeding, with the use of Ad26.COV2.S based on a statistical signal of disproportionate reporting identified within the Company global safety database. Due to these concurrent evaluations involving haemorrhagic disorders, and the previously known important potential risk of Immune Thrombocytopenia (ITP) following Ad26.COV2.S, the Company decided to conduct an aggregate evaluation on haemorrhagic disorders as well as Thrombocytopenia and Associated Haemorrhagic Disorders. The full, cumulative evaluation is provided in Appendix 7.7.

MAH Conclusion: Based on this review, , the cumulative weight of evidence does not suggest a reasonable possibility that Ad26.COV2.S is directly associated with Heavy Menstrual bleeding. Key factors supporting this conclusion include:

- No imbalances observed for heavy menstrual bleeding. during the double blind phase clinical trials.
- Disproportionate reporting was driven from stimulated reporting from the Netherlands, previously evaluated by the Company.

Additional information on the analysis can be found in Appendix 7.7.

16.2.1.1.3. Postural Orthostatic Tachycardia Syndrome

Request: In the second updated Pharmacovigilance Risk Assessment Committee Rapporteur Assessment report (PRAC AR) (PRAC AR Ad26.COV2.S 2023), (procedure number: EU EMEA/H/C/PSUSA/00010916/202208) for the third Ad26.COV2.S PBRER (reporting interval

25 February 2022 to 24 August 2022), circulated on 04 April 2023, the EMA requested the following:

"*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.*"

MAH Conclusion: Altogether, based on all available data, including review of individual case reports with POTS or dizziness postural, there is insufficient information to support an association between the event and Ad26.COV2.S vaccine, with no solid conclusion on any causal relationship or underlying mechanisms. Review of cases in the Company global safety database identified 2 cases that met the case definition for POTS, however with confounding comorbidities. Disproportionality results were not consistent across databases and across terms. The individual MedDRA PT Postural orthostatic tachycardia syndrome met the statistical threshold for disproportionality in both the Company global safety database and EudraVigilance, but not in the WHO VigiBase or FDA VAERS databases. O/E analyses did not show any evidence for an association between POTS and Ad26.COV2.S, with the caveat that available background incidence rates possibly were overinflated, potentially biasing O/E ratios for POTS towards the null.

Additional information on the analysis can be found in Appendix 7.8.

16.2.1.1.4. Appetite Disorders

Request: On 15 March 2023, Ghana Food and Drugs Authority requested the following:

"A review of all adverse events described as "appetite disorders" following the administration of COVID-19 Vaccine worldwide to enable the Authority assess and take regulatory action where necessary.

This is because the Authority has received 35 ICSRs of "appetite disorders" from the deployment of the vaccine in Ghana which is not listed in the summary of product characteristics for COVId 19 vaccine Jansen."

MAH Conclusion: Based on this review, there was insufficient evidence to suggest a reasonable possibility that the event may be causally associated with Ad26.COV2.S. vaccine.

Additional information on the analysis can be found in Appendix 7.9.

16.2.1.1.5. Encephalitis Including Acute Disseminated Encephalomyelitis

On 17 October 2023, a signal of encephalitis including acute disseminated encephalomyelitis (ADEM) with the use of Ad26.COV2.S was identified based on internal review following routine signal detection activities, including individual case review and disproportionality analysis.

Previously, a cumulative review of encephalitis including ADEM was conducted (dated 12 October 2021). Based on that review, it was concluded that there was insufficient evidence that encephalitis including ADEM was associated with the use of Ad26.COV2.S. The key factors supporting the conclusion at the time included: reporting rate well within the background incidence rate in the population and limited number of cases with detailed information to associate the causality with the vaccination and rule out alternative etiology, lack of established biological plausibility, and no numerical imbalance from the two large phase 3 double-blinded, placebo-controlled clinical trials.

MAH conclusion: Based on this review, there was insufficient evidence to suggest a reasonable possibility that Ad26.COV2.S is causally associated with encephalitis including ADEM.

Key factors supporting this decision include:

- No clear mechanism of action identified.
- No cases of encephalitis from pooled safety analyses reported in either active/placebo arm.
- A slight increase in O/E ratio was observed in young adults in the US and EU restricted sensitivity analysis. No increase was observed among adults ≥60. This was not replicated in the Real World Evidence analysis, which showed a lack of evidence of an increased risk in the 1 to 42 days window.
- Within the Company global safety database data, of the 18 cases assessed as BC Levels 1 to 3, only 4 well documented cases were in close temporal association with no confounders. However, 80 cases were not assessable due to limited clinical details (BCC Level 4 and 5). Additionally, 11 (10 primary dose, 1 booster dose) cases occurred outside of the risk window (1 to 42 days).

Additional information on the analysis can be found in Appendix 7.10.

16.2.1.2. Closed Signals That are Categorised as Important Identified Risks

During this reporting interval, the following signal has been closed and categorised as an important identified risk:

16.2.1.2.1. Myocarditis and Pericarditis

Request:

This topic has been reviewed by the Company in the past. New information has been received that warrants a new review of this topic. On 14 February 2023 a signal was identified for Cardiac inflammatory disease (including myocarditis and pericarditis) with the use of COVID-19 vaccine Ad26.COV2.S based on a request from the US Food and Drug Administration to perform a review of the topic. A full evaluation was completed during the previous PBRER (DLP: 24 February 2023) and an appended as late breaking information. (JNJ- 78436735 [Ad26.COV2.S] Vaccine PBRER 2023).

This topic is further discussed in Section 16.3.1.4, Myocarditis and pericarditis.

16.2.1.3. Closed Signals That are Categorised as Important Potential Risks

No closed signals were categorised as important potential risks.

16.2.1.4. Closed Signals That are Identified Risks not Categorised as Important

No closed signals were categorised as identified risks not considered important.

16.2.1.5. Closed Signals That are Potential Risks not Categorised as Important

No closed signals were categorised as potential risks not considered important.

16.3. Evaluation of Risks and New Information

In accordance with GVP Module VII, the Company collectively assesses new information received during the reporting interval from ICSRs (initial and follow-up), clinical studies (if applicable), registries (if applicable), and the literature to determine if the new information changes the characterisation of these risks.

16.3.1. New Information on Important Identified Risks

16.3.1.1. Thrombosis With Thrombocytopenia Syndrome

Introduction

According to the cRMP (version 6.0; dated 25 October 2022), thrombosis with thrombocytopenia syndrome (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 interval and cumulatively which coded to the search criteria provided in Appendix 5.

Results/Discussion

During this reporting interval, a total of 8 (7 medically confirmed and 1 medically unconfirmed) initial, primary dose cases reporting TTS were retrieved. These 8 serious cases reported 28 serious EOI. A single case may report more than 1 EOI.

There were no cases retrieved for booster dose from the search of the Company global safety database.

Post-Marketing Sources (Including Spontaneous and Solicited) Cases

Primary Dose

During this reporting interval, a total of 8 (7 medically confirmed and 1 medically unconfirmed) initial, primary dose cases reporting TTS were retrieved. These 8 serious cases reported 28 serious EOIs.

Cumulatively, 359 (284 medically confirmed and 75 medically unconfirmed) post-marketing, primary dose cases reporting TTS were retrieved. There were 358 serious and 1 nonserious case which reported a total of 1,244 EOIs (1,231 serious, 13 nonserious). A single case may report more than 1 EOI.

An overview of these cases is presented in Table 46.

Table 46: 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 Reporting Interval=8	Number of Cases Received Cumulatively=359[a]
Sex	Male	4	159
	Female	1	166
	NR	3	34
Age (Years)[b]	18 to 35	2	68
Minimum: 20	36 to 50	1	113
Maximum: 54	51 to 64	1	94
Mean: 37.5	≥65	0	45
Median: 38	Adult	1	5
	NR	4	34
Source	Spontaneous	5	339
	Clinical study (noninterventional, solicited)	3	20
Country/Territory	United States	3	198
	Germany	2	51
	Brazil	1	6
	Canada	1	4
	Croatia	1	1
Event Characteristics		**Number of Events=28**	**Number of Events=1,244**
Seriousness (Event Level)[c]	Serious	28	1,231
	Nonserious	0	13
Outcome (Event Level)[c]	Not resolved	10	399
	Fatal	3	182
	NR	15	411

Key: EOI=Event(s) of Interest; NR=Not Reported

a: For the cumulative column, the counts were presented in decreasing order based on the current reporting interval (25 February 2023 to 24 February 2024).

b: The median and mean age calculation were based on the current reporting interval (25 February 2023 to 24 February 2024).

c: Seriousness and outcome have been presented for the EOI. A single case may report more than 1 EOI.

Of these 8 post-marketing, primary dose cases received (≥2), the most frequently reported countries were the US (n=3) and Germany (n=2). These cases concerned 4 males, 1 female, and 3 cases did not report sex. The age range was from 20 to 54 years.

The frequency distribution of the MedDRA PTs of interest reported is presented in Table 47.

Table 47: Frequency Distribution 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 Reporting Interval[a]		Number of Events Reported Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
Thrombosis with thrombocytopenia syndrome	7	0	106	0
Pulmonary embolism	3	0	103	0
Acute myocardial infarction	2	0	10	0
Cerebral infarction	2	0	10	0
Deep vein thrombosis	2	0	72	0
Thrombocytopenia	2	0	184	0
Carotid artery thrombosis	1	0	6	0
Cerebrovascular accident	1	0	24	0
Disseminated intravascular coagulation	1	0	20	0
Haemorrhagic stroke	1	0	8	0
Hepatic vein thrombosis	1	0	8	0
Immune thrombocytopenia	1	0	26	0
Ischaemic stroke	1	0	4	0
Platelet count decreased	1	0	102	10
Renal infarct	1	0	7	0
Thrombosis	1	0	77	0

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

a: The MedDRA PTs of interest have been presented for the reporting interval (25 February 2023 to 24 February 2024).

b: For the cumulative column, the event was presented based on the event counts of the current reporting interval (25 February 2023 to 24 February 2024).

The EOIs reported at a frequency ≥2 in these 8 cases were Thrombosis with thrombocytopenia syndrome (n=7), Pulmonary embolism (n=3), Acute myocardial infarction, Cerebral infarction, Deep vein thrombosis, and Thrombocytopenia (n=2 each). The mean and median Time to Onset (TTO) were 213.9 and 13 days, respectively, and the range was from 13 to 716 days. Of the 28 EOIs, outcomes were reported for 13 as follows: not resolved (n=10) and fatal (n=3).

The Company identified these 8 post-marketing, initial, primary dose cases that met case definition for TTS and are stratified by age group and sex and for BC, Centers for Disease Control (CDC), and Pharmacovigilance Risk Assessment Committee (PRAC) criteria (See Table 48).

Table 48: 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 Interval (Number of Cases=8; Number of Events=28)

Age Group	20 to 35			36 to 50			51 to 54			Adult			NR		
Sex	**F**	**M**	**NR**	**F**	**M**	**NR**	**F**	**M**	**NR**	**F**	**M**	**NR**	**F**	**M**	**NR**
CDC															
Tier 1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Neither	0	1	0	0	1	0	0	1	0	0	0	1	0	1	2
Total	**1**	**1**	**0**	**0**	**1**	**0**	**0**	**1**	**0**	**0**	**0**	**1**	**0**	**1**	**2**
Brighton Collaboration															
Level 1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Level 3	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Level 4	0	1	0	0	1	0	0	0	0	0	0	1	0	1	2
Total	**1**	**1**	**0**	**0**	**1**	**0**	**0**	**1**	**0**	**0**	**0**	**1**	**0**	**1**	**2**
PRAC															
Possible	1	1	0	0	1	0	0	0	0	0	0	1	0	1	2
Unlikely	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Total	**1**	**1**	**0**	**0**	**1**	**0**	**0**	**1**	**0**	**0**	**0**	**1**	**0**	**1**	**2**

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

Booster Dose

There were no cases retrieved for booster from the search of the Company global safety database. No new safety information was identified during the reporting interval for the important identified risk of TTS.

Cumulatively, 7 medically confirmed and 1 medically unconfirmed case reported as booster were identified. These 8 serious cases reported a total of 30 serious EOIs. All these cases were heterologous.

Clinical Trial Cases

No cases were retrieved from either the Janssen-sponsored clinical or Janssen-supported clinical studies during the reporting interval.

Literature ICSR

ICSR literature cases received during the current reporting interval were reviewed and no information was identified that would change the information known about TTS.

Line Listings

Death: During the current reporting interval (25 February 2023 to 24 February 2024), 1 fatal case was retrieved. This case reported 3 fatal EOIs.

A CIOMS II LL of the fatal case is presented in Appendix 7.11.1. Additional information on the fatal case can also be found in Appendix 7.26, Death.

Booster: A cumulative CIOMS II LL of cases reported as booster is presented in Appendix 7.11.2.

Conclusion

Based on the evaluation of the cases, and review of safety data from other sources, the information is consistent with the information known about TTS.

16.3.1.2. Guillain-Barré syndrome

Introduction

According to the cRMP (version 6.0, dated 25 October 2022), Guillain-Barré Syndrome (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 interval and cumulatively, which coded to the search criteria provided in Appendix 5.

Results/Discussion

During this reporting interval, a total of 29 (17 medically confirmed and 12 medically unconfirmed) initial, primary dose cases reporting GBS were retrieved. All cases were serious and reported a total of 37 serious EOIs.

During this reporting interval, a total of 2 (1 medically confirmed and 1 medically unconfirmed) initial cases reported as booster were identified. Both cases were serious and reported a total of 2 serious EOIs. Both cases were homologous.

Post-marketing Sources (Including Spontaneous and Solicited) Cases

Primary Dose

During this reporting interval, a total of 28 (16 medically confirmed and 12 medically unconfirmed) post-marketing, initial, primary dose cases reporting GBS were retrieved. All cases were serious and reported a total of 36 serious EOIs.

Cumulatively, 656 (370 medically confirmed and 286 medically unconfirmed) post-marketing, primary dose cases reporting GBS were retrieved. All cases were serious and reported a total of 702 serious EOIs.

An overview of these cases is presented in Table 49.

Table 49: Characteristics of Post-marketing Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Guillain-Barré Syndrome

Case Characteristics		Number of Cases Received During the Reporting Interval=28	Number of Cases Received Cumulatively=656[a]
Sex	Male	14	386
	Female	7	230
	NR	7	40
Age (Years)[b]	18 to 35	3	75
Minimum: 22	36 to 50	5	181
Maximum: 67	51 to 64	7	246
Mean: 49. 8	≥65	3	86
Median: 51.5	Adult	1	6
	Elderly	0	2
	NR	9	60
Source	Spontaneous	20	646
	Clinical study (noninterventional, solicited)	8	10
Country/Territory[c]	United States	5	336
	Spain	4	28
	France	3	22
	Germany	3	92
	Korea, Republic of	3	22
	Portugal	2	14
Event Characteristics		**Number of Events=36**	**Number of Events=702**
Seriousness (Event Level)[d]	Serious	36	702
Outcome (Event Level)[d]	Not resolved	11	324
	Resolved with sequelae	7	33
	Resolving	7	128
	NR	11	175

Key: Ad26.COV2.S: Adenovirus Type 26.Coronavirus 2.Spike EOI=Event(s) of Interest; NR=Not Reported

a: For the cumulative column, the counts were presented in the decreasing order based on the current reporting interval (25 February 2023 to 24 February 2024).

b: The median and mean age calculation were based on the current reporting interval (25 February 2023 to 24 February 2024).

c: Countries/territories with frequency ≥2 were presented in the decreasing order for the current reporting interval (25 February 2023 to 24 February 2024).

d: Seriousness and outcome have been presented for the events based on the current reporting interval (25 February 2023 to 24 February 2024). A single case may report more than 1 EOI.

Of the 28 post-marketing primary dose cases received, the most frequently reported countries/territories of origin (n≥2) were the US (n=5); Spain (n=4); France, Germany, and Republic of Korea, Republic of (n=3 each); and Portugal (n=2). These cases concerned 14 males, 7 females, and 7 did not report sex. The age range was from 22 to 67 years.

The frequency distribution of the MedDRA PTs of interest reported is presented in Table 50.

Table 50: Frequency Distribution of MedDRA PTs of Interest in Post-marketing Primary Dose Cases Reporting Guillain-Barré Syndrome With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Reporting Interval[a]		Number of Events Reported Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
Guillain-Barré syndrome	22	0	590	0
Chronic inflammatory demyelinating polyradiculoneuropathy	7	0	56	0
Demyelinating polyneuropathy	3	0	20	0
Miller Fisher syndrome	2	0	21	0
Acute motor axonal neuropathy	1	0	3	0
Bickerstaff's encephalitis	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 interval (25 February 2023 to 24 February 2024). A single case may report more than 1 Me5dDRA PT.
b: For the cumulative column, the events were presented in decreasing order based on the event counts of the current reporting interval (25 February 2023 to 24 February 2024).

The EOIs included GBS (n=22), chronic inflammatory demyelinating polyradiculoneuropathy (n=7), demyelinating polyneuropathy (n=3), Miller Fisher syndrome (n=2), and Acute motor axonal neuropathy and Bickerstaff's encephalitis (n=1 each). The mean and median TTO were 132.3 and 18.5 days, respectively, and the range was from 0 to 620 days. Of the 36 EOIs, outcomes were reported for 25 and are as follows: not resolved (n=11) and resolving and resolved with sequelae (n=7 each).

Booster Dose

During this reporting interval, a total of 2 (1 medically confirmed and 1 medically unconfirmed) initial, post-marketing cases reported as booster were identified. Both cases were serious and reported a total of 2 serious EOIs. Both cases were homologous.

Cumulatively, 19 (6 medically confirmed and 13 medically unconfirmed) cases reported as booster were identified. All cases were serious and reported a total of 19 serious EOIs. Of these cases, 11 were heterologous and 8 were homologous.

An overview of these cases is presented in Table 51.

Table 51: Characteristics of Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Guillain-Barré Syndrome

Case Characteristics		Number of Cases Received During the Reporting Interval=2	Number of Cases Received Cumulatively=19[a]
Sex	Male	1	10
	Female	1	8
Age (Years)[b]	≥65	1	6
Minimum: NA	NR	1	3
Maximum: 69			
Mean: 69			
Median: 69			
Source	Spontaneous	1	17
	Clinical study (noninterventional, solicited)	1	2
Country/Territory	Portugal	1	2
	United States	1	4
Classification	Homologous	2	8
Event Characteristics		**Number of Events=2**	**Number of Events=19**
Seriousness (Event Level)[c]	Serious	2	19
Outcome (Event Level)[c]	Resolving	1	5
	NR	1	7

Key: EOI=Event(s) of Interest; NR=Not Reported

a: For the cumulative column, the counts were presented in decreasing order based on the current reporting interval (25 February 2023 to 24 February 2023).

b: The median and mean age calculations were based on the current reporting interval (25 February 2023 to 24 February 2024).

c: Seriousness and outcome have been presented for the EOI.

Of these 2 post-marketing cases reported as booster, Portugal and US were the reported countries/territories of origin (n=1 each). These cases concerned 1 female and 1 male. The age for 1 case was reported as 69 years and was not reported for other case.

The frequency distribution of the MedDRA PTs of interest reported in post-marketing cases reported as booster is presented in Table 52.

Table 52: Frequency Distribution of MedDRA PTs of Interest in Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Guillain-Barré Syndrome

MedDRA PTs	Number of Events Reported During the Reporting Interval[a]		Number of Events Reported Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
Guillain-Barré syndrome	2	0	15	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 current reporting interval (25 February 2023 to 24 February 2024).
b: For the cumulative column, the events were presented in decreasing order based on the event counts of the current reporting interval (25 February 2023 to 24 February 2024).

The EOI included GBS (n=2). The TTO was not reported in both cases. Of the 2 EOIs, outcomes were reported for 1 and was resolving (n=1).

Clinical Trial Cases

During this reporting interval, 1 clinical case (primary dose, no booster) was retrieved from a Janssen-supported Clinical Trial and no cases were retrieved from Janssen-sponsored Clinical Studies.

Janssen-supported Clinical Studies

During this reporting interval, 1 primary dose case reporting GBS was retrieved from a Janssen-supported Clinical Study. This case was from protocol number VAC31518COV3021. This case was reported from South Africa and concerned a [redacted]-year-old female reporting 1 serious EOI of GBS, and the outcome of the event was resolved with sequelae. The TTO was 42 days.

During this reporting interval, no cases reported as booster were retrieved from Janssen-supported Clinical Studies.

Janssen-sponsored Clinical Studies

During this reporting interval, no case reporting GBS as primary and booster dose was retrieved from Janssen-sponsored Clinical Studies.

Literature ICSR

ICSR literature cases received during the current reporting interval were reviewed, and no information was identified that would change the information known about GBS.

Line Listings

Death: During the current reporting interval (25 February 2023 to 24 February 2024), a total of 3 fatal cases were retrieved. However, none of these cases reported a fatal EOI.

A CIOMS II LL of the fatal cases is presented in Appendix 7.12.1. Additional information on the fatal cases can also be found in Appendix 7.26, Death.

Booster: A cumulative CIOMS II LL of cases reported as booster is presented in Appendix 7.12.2.

Conclusion

Based on the evaluation of the cases and review of safety data from other sources, the information is consistent with what is currently known about GBS.

16.3.1.3. Venous Thromboembolism

Introduction

According to the cRMP (version 6.0, dated 25 October 2022), Venous Thromboembolism (VTE) 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 interval and cumulatively, which were coded to the search criteria provided in Appendix 5.

Results/Discussion

During this reporting interval, a total of 68 (38 medically confirmed and 30 medically unconfirmed) initial, primary dose cases reporting VTE were retrieved. There were 66 serious and 2 nonserious cases, which reported a total of 87 EOI (82 serious and 5 nonserious).

During this reporting interval, a total of 16 (13 medically confirmed and 3 medically unconfirmed) initial cases reported as booster cases reporting VTE were retrieved. There were 14 serious and 2 nonserious cases, which reported a total of 18 EOI (16 serious and 2 nonserious). All these cases were homologous cases.

Post-marketing Sources (Including Spontaneous and Solicited) Cases

Primary Dose

During this reporting interval, a total of 61 (31 medically confirmed and 30 medically unconfirmed) post-marketing, initial, primary dose cases reporting VTE were retrieved. There were 60 serious and 1 nonserious case, which reported a total of 79 EOI (76 serious; 3 nonserious).

Cumulatively, 2,255 (1,535 medically confirmed and 720 medically unconfirmed) post-marketing, primary dose cases reporting VTE were retrieved. There were 2,173 serious and 82 nonserious cases, which reported a total of 2,914 EOI (2,801 serious, 113 nonserious).

An overview of these cases is presented in Table 53.

Table 53: Characteristics of Post-marketing Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Venous Thromboembolism

Case Characteristics		Number of Cases Received During the Interval Reporting Interval=61	Number of Cases Received Cumulatively=2,255[a]
Sex	Female	32	1,067
	Male	23	1,115
	NR	6	73
Age (Years)[b]	18 to 35	9	286
Minimum: 20	36 to 50	10	599
Maximum: 93	51 to 64	14	746
Mean: 57.12	≥65	18	504
Median: 60	Adult	2	17
	NR	8	99
Source	Spontaneous	57	2,227
	Clinical study (noninterventional, solicited)	4	28
Country/Territory[c]	United States	38	1,556
	Germany	10	232
	France	3	75
Event Characteristics		**Number of Events=79**	**Number of Events=2,914**
Seriousness (Event Level)[d]	Serious	76	2,801
	Nonserious	3	113
Outcome (Event Level)[d]	Not resolved	13	1,233
	Resolved	11	364
	Fatal	4	182
	Resolving	3	312
	Resolved with sequelae	3	31
	NR	45	792

Key: EOI=Event(s) of Interest; NR=Not Reported

a: For the cumulative column, the counts were presented in the decreasing order based on the current reporting interval (25 February 2023 to 24 February 2024).

b: The median and mean age calculation were based on the current reporting interval (25 February 2023 to 24 February 2024). The age group was presented for cases where age was not reported.

c: Countries/territories with frequency ≥3 was presented in the decreasing order for the current reporting interval (25 February 2023 to 24 February 2024).

d: Seriousness and outcome have been presented for the EOI. A single case may report more than 1 EOI.

Of these 61 post-marketing, primary dose cases received, the most frequently reported countries/territories of origin (n≥3) were the US (n=38), Germany (n=10), and followed by France (n=3). These cases concerned 32 females, 23 males, and 6 did not report sex. The age range was from 20 to 93 years.

The frequency distribution of the MedDRA PTs of interest reported is presented in Table 54.

Table 54: Frequency Distribution of MedDRA PTs of Interest in Post-marketing Primary Dose Cases Reporting Venous Thromboembolism With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Interval Reporting Interval[a]		Number of Events Reported Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
Pulmonary embolism	30	0	990	1
Deep vein thrombosis	24	0	829	1
Pulmonary thrombosis	5	0	195	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 the decreasing order for the reporting interval (25 February 2023 to 24 February 2024). A single case may report more than 1 MedDRA PT of interest.
b: For the cumulative column, the events were presented in the decreasing order based on the event counts of the current reporting interval (25 February 2023 to 24 February 2024).

The EOI reported at a frequency ≥5 included pulmonary embolism (n=30), deep vein thrombosis (n=24), and pulmonary thrombosis (n=5). The mean and median TTO were 177.2 and 85 days, respectively, and the range was from 0 to 803 days. Of the 79 EOI, outcomes were reported for 34 and are as follows: not resolved (n=13), resolved (n=11), fatal (n=4), resolving and resolved with sequelae (n=3 each).

Booster Dose

During this reporting interval, a total of 15 (12 medically confirmed and 3 medically unconfirmed) initial cases reported as booster were retrieved. There were 14 serious and 1 nonserious case, which reported a total of 17 EOI (16 serious; 1 nonserious). All these cases were homologous.

Cumulatively, a total of 89 (55 medically confirmed and 34 medically unconfirmed) cases reported as booster were identified. Of the 89 cases, 88 were serious and 1 was nonserious. These 89 cases reported a total of 113 EOI (112 serious; 1 nonserious). Of these cases, 62 were homologous and 27 were heterologous.

An overview of these cases is presented in Table 55.

Table 55: Characteristics of Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Venous Thromboembolism

Case Characteristics		Number of Cases Received During the Reporting Interval=15	Number of Cases Received Cumulatively=89[a]
Sex	Male	10	54
	Female	5	32
Age (Years)[b]	18 to 35	1	7
Minimum: 29	36 to 50	2	27
Maximum: 81	51 to 64	7	20
Mean: 59.4	≥65	5	29
Median: 60			

Table 55: Characteristics of Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Venous Thromboembolism

Case Characteristics		Number of Cases Received During the Reporting Interval=15	Number of Cases Received Cumulatively=89[a]
Source	Spontaneous	15	85
Country/Territory	United States	10	55
	Germany	2	11
	Austria	1	2
	France	1	2
	Spain	1	1
Classification	Homologous	15	62
	Heterologous	0	27
Event Characteristics		**Number of Events=17**	**Number of Events=113**
Seriousness (Event Level)[c]	Serious	16	112
	Nonserious	1	1
Outcome (Event Level)[c]	Not resolved	2	25
	Fatal	1	4
	Resolved	1	20
	NR	13	49

Key: EOI=Event(s) of Interest; NR=Not Reported
a: For the cumulative column, the counts were presented in the decreasing order based on the current reporting interval (25 February 2023 to 24 February 2024).
b: The median and mean age calculations were based on the current reporting interval (25 February 2023 to 24 February 2024).
c: Seriousness and outcome have been presented for the EOI. A single case may report more than 1 EOI.

Of these 15 post-marketing cases reported as booster, reported countries/territories of origin were the US (n=10); Germany (n=2); followed by Austria, France, and Spain (n=1 each). These cases concerned 10 males and 5 females. The age range was from 29 to 81 years.

The frequency distribution of the MedDRA PTs of interest reported in post-marketing cases reported as booster is presented in Table 56.

Table 56: Frequency Distribution of MedDRA PTs of Interest in Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Venous Thromboembolism

	Number of Events Reported During the Interval Reporting Interval[a]		Number of Events Reported Cumulatively[b]	
MedDRA PTs	**Serious**	**Nonserious**	**Serious**	**Nonserious**
Pulmonary embolism	7	0	32	0
Deep vein thrombosis	4	0	40	0
Thrombophlebitis	1	1	1	1
Budd-Chiari syndrome	1	0	1	0

Table 56: Frequency Distribution of MedDRA PTs of Interest in Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Venous Thromboembolism

	Number of Events Reported During the Interval Reporting Interval[a]		Number of Events Reported Cumulatively[b]	
MedDRA PTs	**Serious**	**Nonserious**	**Serious**	**Nonserious**
Central venous catheterisation	1	0	3	0
Pelvic venous thrombosis	1	0	2	0
Renal vein thrombosis	1	0	1	0

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

a: The MedDRA PTs of interest are sorted and presented by decreasing order for the current reporting interval (25 February 2023 to 24 February 2024). A single case may report more than 1 MedDRA PT of interest.

b: For the cumulative column, the events were presented in decreasing order based on the event counts of the current reporting interval (25 February 2023 to 24 February 2024).

The EOI included pulmonary embolism (n=7); deep vein thrombosis (n=4); thrombophlebitis (n=2); and Budd-Chiari syndrome, central venous catheterisation, pelvic venous thrombosis, and renal vein thrombosis (n=1 each). The mean and median TTO were 259.3 and 268 days, respectively, and the range was from 2 to 518 days. Of the 17 EOI, outcomes were reported for 4 EOI and are as follows: not resolved (n=2) and fatal and resolved (n=1 each).

Epidemiology Data

A retrospective cohort study was conducted to estimate the association between the first dose of JCOVDEN (vs. mRNA) vaccine and VTE among women aged 18 to 49 years across 5 the United States administrative claims databases licensed by the Company between 2021 and 2023. Details of the study are presented in Appendix 7.13.

Clinical Trial Cases

During this reporting interval, a total of 8 clinical cases (7 primary dose and 1 booster) were retrieved from Janssen-sponsored and Janssen-supported Clinical Studies.

Janssen-sponsored Clinical Studies

During this reporting interval, a total of 3 primary dose cases reporting VTE were retrieved from Janssen-sponsored Clinical Studies. Of the 3 cases, 2 were from VAC31518COV3009 and 1 from VAC31518COV3001. These 3 cases concerned male patients and reported 4 EOI (2 serious, 2 nonserious). Of these 3 cases, 2 were reported from the US and 1 was reported from the UK. The age range was from 64 to 75 years.

The EOI reported in these cases were pulmonary embolism (n=2) and deep vein thrombosis and superficial vein thrombosis (n=1 each). The mean and median TTO were 563.7 and 700 days, and the range was from 291 to 700 days. The reported outcomes of the EOI are as follows: not resolved (n=2) and resolved and resolving (n=1 each).

During this reporting interval, a total of 1 booster case reporting VTE was retrieved from Janssen-sponsored Clinical Studies. This case was reported from VAC31518COV3009 and concerned a 46-year-old female from [redacted] who experienced a nonserious EOI of superficial vein thrombosis. The TTO was 709 days, and the reported outcome was resolved.

Janssen-supported Clinical Studies Cases

During this reporting interval, 4 primary dose cases reporting VTE was retrieved from a Janssen-supported Clinical Study. Three cases were reported from VAC31518COV3021, and 1 case was reported from VAC31518COV3012. These 4 cases reported 4 serious EOI. All cases were reported from South Africa. These cases concerned 3 females and 1 male. The age range was from 37 to 59 years.

The EOI reported in these cases were deep vein thrombosis and pulmonary embolism (n=2 each). The mean and median TTO were 136.5 and 96 days, respectively, and the range was from 7 to 347 days. The outcomes of the EOI are as follows: resolved (n=2) and resolved with sequelae and unknown (n=1 each).

During this reporting interval, no cases reported as booster were retrieved from Janssen-supported Clinical Studies.

Literature ICSR

ICSR literature cases received during the current reporting interval were reviewed, and no information was identified that would change the information known about VTE.

Line Listings

Death: During the current reporting interval (25 February 2023 to 24 February 2024), a total of 5 fatal cases were retrieved. Of these cases, 4 cases reported fatal EOI.

A CIOMS II LL of the fatal cases is presented in Appendix 7.13.1. Additional information on the fatal cases can also be found in Appendix 7.26, Death.

Booster: A cumulative CIOMS II LL of cases reported as booster is presented in Appendix 7.13.2.

Conclusion

Based on the evaluation of the cases and review of safety from other sources, the information is consistent with what is currently known about VTE.

16.3.1.4. Myocarditis and pericarditis

Introduction

Myocarditis and pericarditis was an AESI in the previous PBRER (DLD of 24 February 2023). The cRMP (version 8.0, dated 06 February 2024) and EU-RMP (7.1 version) includes myocarditis and pericarditis as 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 interval and cumulatively, which coded to the MedDRA High Level Terms (HLTs): Noninfectious myocarditis, Noninfectious pericarditis provided in Appendix 5.

Results/Discussion

During this reporting interval, a total of 21 (12 medically confirmed and 9 medically unconfirmed), primary dose cases reporting myocarditis and pericarditis were retrieved. These 21 serious cases reported a total of 23 serious EOIs.

During this reporting interval, a total of 8 (7 medically confirmed and 1 medically unconfirmed) booster cases reporting myocarditis and pericarditis were retrieved. All the 8 cases were serious and reported a total of 10 serious EOIs. All 8 cases were heterologous.

Post-marketing Sources (Including Spontaneous and Solicited) Cases

Primary Dose

During this reporting interval, a total of 20 (11 medically confirmed and 9 medically unconfirmed) post-marketing, initial, primary dose cases reporting myocarditis and pericarditis were retrieved. All these 20 cases were serious and reported a total of 22 serious EOIs.

Cumulatively, 458 (263 medically confirmed and 195 medically unconfirmed) post-marketing, primary dose cases reporting myocarditis and pericarditis were retrieved. All the 458 cases were serious and reported a total of 481 serious EOIs.

An overview of these cases is presented in Table 57.

Table 57: Characteristics of Post-marketing Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Myocarditis and Pericarditis

Case Characteristics		Number of Cases Received During the Reporting Interval=20	Number of Cases Received Cumulatively=458[a]
Sex	Male	11	292
	Female	6	134
	NR	3	32
Age (Years)[b]	18 to 35	5	187
Minimum: 19	36 to 50	6	91
Maximum: 74	51 to 64	3	107
Mean: 44.4	≥65	2	28
Median: 48	Adult	1	6
	NR	3	38
Source	Spontaneous	19	453
	Clinical study (noninterventional, solicited)	1	5

Table 57: Characteristics of Post-marketing Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Myocarditis and Pericarditis

Case Characteristics		Number of Cases Received During the Reporting Interval=20	Number of Cases Received Cumulatively=458[a]
Country/Territory[c]	United States	6	214
	Germany	3	82
	Netherlands	2	31
Event Characteristics		**Number of Events of Interest=22**	**Number of Events of Interest=481**
Seriousness (Event Level)[d]	Serious	22	481
Outcome (Event Level)[d]	Not resolved	5	164
	Resolved	4	72
	Resolving	4	68
	Resolved with sequelae	2	15
	Fatal	1	19
	NR	6	143

Key: EOI=Event(s) of Interest; NR=Not Reported
a: For the cumulative column, the counts are presented in decreasing order based on the current reporting interval (25 February 2023 to 24 February 2024).
b: The median and mean age calculation are based on the current reporting interval (25 February 2023 to 24 February 2024). Age group is presented for cases where age was not reported.
c: Countries/territories with frequency ≥2 were presented in the decreasing order for the current reporting interval (25 February 2023 to 24 February 2024).
d: A single case may report more than 1 EOI.

Of these 20 post-marketing, primary dose cases received during the reporting interval, the most frequently reported countries/territories of origin ≥2 were the US (n=6), Germany (n=3), and Netherlands (n=2). These cases concerned 11 males, 6 females, and 3 did not report sex. The age range was from 19 to 74 years.

The frequency distribution of the reported MedDRA PTs of interest is presented in Table 58.

Table 58: Frequency Distribution of MedDRA PTs of Interest in Post-marketing Primary Dose Cases Reporting Myocarditis and Pericarditis With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Reporting Interval[a]		Number of Events Reported Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
Myocarditis	13	0	234	0
Pericarditis	7	0	206	0
Myopericarditis	2	0	34	0

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: A single case may report more than 1 MedDRA PT of interest.
b: For the cumulative column, the events were presented in the decreasing order based on the event counts of the current reporting interval (25 February 2023 to 24 February 2024).

The reported EOIs included myocarditis (n=13), pericarditis (n=7), and myopericarditis (n=2). The mean and median TTO were 171.1 and 32 days, respectively, and the range was from Day 0 to

735 days. Of the 22 EOIs, outcomes were reported for 16 and are as follows: not resolved (n=5), resolved (n=4), resolving (n=4), resolved with sequelae (n=2), and fatal (n=1).

Booster Dose

During this reporting interval, a total of 8 (7 medically confirmed and 1 medically unconfirmed) cases reported as booster were identified. All 8 cases were serious. These 8 cases reported a total of 10 serious EOIs. Of these 8 cases, 7 were heterologous and 1 was homologous.

Cumulatively, a total of 41 (16 medically confirmed and 25 medically unconfirmed) cases reported as booster were identified. All 41 cases reported were serious. These 41 cases reported a total of 46 serious EOIs. Of these 41 cases, 20 were homologous and 21 were heterologous.

An overview of these cases is presented in Table 59.

Table 59: Characteristics of Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Myocarditis and Pericarditis

Case Characteristics		Number of Cases Received During the Reporting Interval=8	Number of Cases Received Cumulatively=41[a]
Sex	Male	6	28
	Female	1	8
	NR	1	5
Age (Years)[b] **Minimum: 18** **Maximum: 68** **Mean: 34.9** **Median: 30.5**	18 to 35 36 to 50 ≥65	4 3 1	14 12 3
Source	Spontaneous	8	38
Country/Territory	Iceland	5	5
	Germany	1	10
	Italy	1	1
	South Africa	1	3
Classification	Heterologous	7	21
	Homologous	1	20
Event Characteristics		**Number of Events of Interest=10**	**Number of Events of Interest=46**
Seriousness (Event Level)[c]	Serious	10	46
Outcome (Event Level)[c]	Not resolved	1	9
	Resolved with sequelae	1	2
	NR	8	24

Key: EOI=Event(s) of Interest; NR=Not Reported

a: For the cumulative column, the counts were presented in the decreasing order based on the current reporting interval (25 February 2023 to 24 February 2024).

b: The median and mean age calculations were based on the current reporting interval (25 February 2023 to 24 February 2024).

c: A single case may report more than 1 EOI.

Of these 8 post-marketing booster cases, reported countries/territories of origin were as follows: Iceland (n=5), Germany, Italy, and South Africa (n=1 each). These cases concerned 6 males, 1 female, and 1 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 booster cases is presented in Table 60.

Table 60: Frequency Distribution of MedDRA PTs in Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Myocarditis and Pericarditis

MedDRA PTs	Number of Events Reported During the Reporting Interval[a]		Number of Events Reported Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
Pericarditis	6	0	17	0
Myocarditis	3	0	28	0
Myopericarditis	1	0	1	0

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: The MedDRA PTs of interest are sorted and presented by the decreasing order for the current reporting interval (25 February 2023 to 24 February 2024). A single case may report more than 1 MedDRA PT.
b: For the cumulative column, the events were presented in the decreasing order based on the event counts of the current reporting interval (25 February 2023 to 24 February 2024).

The reported EOIs included pericarditis (n=6), myocarditis (n=3), and myopericarditis (n=1). The mean and median TTO were 73.6 and 43 days, respectively, and the range was from 4 to 205 days. Of the 10 EOIs, outcomes were reported for 2 and are as follows: not resolved (n=1) and resolved with sequelae (n=1).

Clinical Trial Cases

During this reporting interval, a total of 1 clinical case (primary dose) was retrieved from Janssen-sponsored and Janssen-supported Clinical Studies.

Janssen-sponsored Clinical Studies

During this reporting interval, a total of 1 primary dose case reporting myocarditis was retrieved from Janssen-sponsored Clinical Studies. This case was from VAC31518COV3009 and concerned a 44-year-old male from [redacted] This case reported 1 serious EOI of myocarditis, and the outcome of the EOI was not resolved.

During this reporting interval, no case reported as booster was retrieved from Janssen-sponsored Clinical Studies.

Janssen-supported Clinical Studies Cases

During this reporting interval, no case reported as primary dose was retrieved from Janssen-supported Clinical Studies.

During this reporting interval, no case reported as booster was retrieved from Janssen-supported Clinical Studies.

Literature ICSR

ICSR literature cases received during the current reporting interval were reviewed, and no information was identified that would change the information known about myocarditis and pericarditis.

Line Listings

Death: During the current reporting interval (25 February 2023 to 24 February 2024), a total of 1 fatal case (primary dose) was retrieved. This case reported 1 fatal EOI.

A CIOMS II LL of the fatal cases is presented in Appendix 7.14.1. Additional information on the fatal cases can also be found in Appendix 7.26, Death.

Booster: A cumulative CIOMS II LL of cases reported as booster is presented in Appendix 7.14.2.

Conclusion

Based on the evaluation of the cases and review of safety data from other sources, the information is consistent with what is currently known about myocarditis and pericarditis.

16.3.1.5. Thrombocytopenia (Including Immune Thrombocytopenia)

Introduction

According to the cRMP (version 6.0, dated 25 October 2022), immune thrombocytopenia is an important potential risk associated with the use of Ad26.COV2.S which was reclassified as an important identified risk and renamed to "Thrombocytopenia, including immune thrombocytopenia" in cRMP version 8.0. In the EU-RMP (version 5.3, dated 13 February 2023), 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 interval and cumulatively which coded to the search criteria provided in Appendix 5.

The case definition for this topic is described within as follows: 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 version 10.16.3 for thrombocytopenia (Brighton Collaboration 2021a). It should be noted that there are no BC criteria for ITP. Cases were then further screened using a case definition modified from the American Society of Haematology (ASH) (Kelton 2018), and only cases meeting the definition for confirmed, likely, and suspected were included. It is acknowledged that the threshold appears very high for a case to be able to fulfil the definition of “confirmed” (see Table 61).

Table 61: Summary of ASH Case Definition for Thrombocytopenia, including immune thrombocytopenia

	Platelet	Treatment	Antiplatelet 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 antiplatelet 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 antiplatelet 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 Haematology; IVIG=Intravenous Immunoglobulin

Results/Discussion

During this reporting interval, a total of 119 (115 medically confirmed and 4 medically unconfirmed) initial, primary dose cases reporting thrombocytopenia, including immune thrombocytopenia were retrieved. There were 24 serious and 95 nonserious cases, which reported a total of 122 EOIs (24 serious, 98 nonserious).

During this reporting interval, a total of 25 medically confirmed (no medically unconfirmed) initial cases reported as booster were identified. There were 1 serious and 24 nonserious cases which reported a total of 25 EOIs (1 serious and 24 nonserious). Of these cases 24 were homologous and 1 did not provide individual patient details.

Post-marketing Source (including spontaneous and solicited) Cases

Primary Dose

During this reporting interval, a total of 20 (16 medically confirmed and 4 medically unconfirmed) post-marketing, primary dose cases reporting thrombocytopenia, including immune thrombocytopenia were retrieved. All cases were serious and included a total of 23 serious EOIs. Out of these 20 cases, 8 cases were assessed as ITP cases per ASH case definition.

Cumulatively, 861 (626 medically confirmed and 235 medically unconfirmed) post-marketing, primary dose cases reporting thrombocytopenia, including immune thrombocytopenia were retrieved. There were 742 serious and 119 nonserious cases, which reported a total of 1,010 EOIs

(859 serious, 151 nonserious). Out of 861 cases, 429 cases were assessed as ITP cases per ASH case definition.

An overview of these cases is presented in Table 62.

Table 62: Characteristics of Post-marketing Primary Dose Cases Involving the Use of Ad26.COV2.S and Assessed as Thrombocytopenia, including immune thrombocytopenia

Case Characteristics		Number of Cases Received During the Interval Reporting Interval=8	Number of Cases Received Cumulatively=429[a]
Sex	Male	6	220
	Female	2	204
Age (Years)[b] **Minimum: 21** **Maximum: 67** **Mean: 37.4** **Median: 37**	18 to 35	3	3
	36 to 50	4	158
	≥65	1	77
Source	Spontaneous	8	425
Country/Territory	Germany	3	44
	Poland	2	0[d]
	India	1	0[d]
	Netherlands	1	0[d]
	Spain	1	0[d]
Event Characteristics		**Number of Events=8**	**Number of Events=493**
Seriousness (Event Level)[c]	Serious	8	374
Outcome (Event Level)[c]	Not resolved	4	157
	Resolving	1	0[d]
	Resolved	1	84
	NR	2	183

Key: EOI=Event(s) of Interest; NR=Not Reported

a: For the cumulative column, the counts were presented in decreasing order based on the current reporting interval (25 February 2023 to 24 February 2024).

b: The median and mean age calculations were based on the current reporting interval (25 February 2023 to 24 February 2024).

c: Seriousness and outcome have been presented for the EOI. A single case may report more than 1 EOI.

d: The data for countries reported as zero and outcome reported as zero in cumulative counts is not available for the cases qualifying ASH criteria. Hence, these are presented as 0 for presentation purpose.

Of these 8 cases received, the reported countries/territories of origin were Germany (n=3); Poland (n=2); and India, Netherlands, and Spain (n=1 each). These cases concerned 6 males and 2 females. The age range was from 21 to 67 years.

The frequency distribution of the MedDRA PTs of interest reported is presented in Table 63.

Table 63: Frequency Distribution of MedDRA PTs of Interest in Post-marketing Primary Dose Cases Assessed as Thrombocytopenia, including immune thrombocytopenia With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Reporting Interval[a]		Number of Events Reported Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
Thrombocytopenia	6	0	149	0
Immune thrombocytopenia	2	0	84	0

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: The MedDRA PTs have been presented and sorted by decreasing order for the reporting interval (25 February 2023 to 24 February 2024). A single case may report more than 1 MedDRA PT.
b: For the cumulative column, the events were presented in decreasing order based on the event counts of the current reporting interval (25 February 2023 to 24 February 2024).

The EOIs included thrombocytopenia (n=6) and immune thrombocytopenia (n=2). The mean and median TTO were 13.25 and 13 days, respectively, and the range was from 13 to 14 days. Of the 8 EOIs, outcomes were reported for 6 and are as follows: not resolved (n=4), resolving (n=1), and resolved (n=1).

Booster Dose

During this reporting interval, 1 serious medically confirmed (no medically unconfirmed) initial case reported as booster was identified. This case pertaining to multiple patients, information regarding individual patients was not reported and also did not qualify as ITP per ASH case definition, hence is not discussed further.

Cumulatively, 24 (14 medically confirmed and 10 medically unconfirmed) cases reported as booster were identified. There were 21 serious and 3 nonserious cases which reported a total of 25 EOI (16 serious, 9 nonserious). Of these cases, 11 were heterologous and 12 were homologous and in the remaining case pertaining to multiple patients, information regarding individual patients was not reported. Out of 24 cases, 17 cases were assessed as ITP cases per ASH case definition.

Clinical Trial Cases

During this reporting interval, a total of 123 clinical cases (99 primary and 24 booster) were retrieved from Janssen-sponsored Clinical Studies. Of these 123 clinical cases (99 primary and 24 booster), 27 primary dose cases and 14 booster cases were assessed as ITP cases as per ASH criteria. These cases are presented below. No cases were retrieved from Janssen-supported Clinical Studies.

Janssen-sponsored Clinical Studies

During this reporting interval, a total of 27 primary dose cases reporting thrombocytopenia, including immune thrombocytopenia were retrieved from Janssen-sponsored Clinical Studies. Of the 27 cases, 26 were reported from VAC31518COV3009 and 1 was reported from VAC31518COV3001. These 27 cases reported 27 EOIs (26 nonserious and 1 serious). Of these 27 cases, the reported countries/territories of origin were the US (n=8); South Africa (n=5);

Colombia, Philippines, and Spain (n=4 each); and Brazil and France (n=1 each). These cases concerned 18 males and 9 females. The age range was from 18 to 82 years. The EOIs included thrombocytopenia (n=22) and platelet count decreased (n=5). The mean and median TTO were 11.04 and 0 days, respectively, and the range was from 0 to 123 days. Of the 27 EOIs, outcomes were reported for 18 and are as follows: resolved (n=15), resolving (n=2), and not resolved (n=1).

During this reporting interval, a total of 14 cases reported as booster were retrieved from Janssen-sponsored Clinical Studies. All cases were reported from VAC31518COV3009. These 14 cases reported 14 nonserious EOIs. Of these 14 cases, the countries/territories of origin were the US (n=10), Colombia (n=2), and France and South Africa (n=1). These cases concerned 9 males and 5 females. The age range was from 26 to 69 years. The EOIs included thrombocytopenia (n=8) and platelet count decreased (n=6). The mean and median TTO were 95.8 and 95 days, respectively, and the range was from 68 to 122 days. The outcomes were reported as resolved (n=5), resolving (n=2), and not resolved (n=1).

Janssen-supported Clinical Studies Cases

During this reporting interval, there were no cases retrieved from Janssen-supported Clinical Studies.

Literature ICSR

ICSR literature cases received during the current reporting interval were reviewed, and no information was identified that would change the information known about thrombocytopenia, including immune thrombocytopenia.

Line Listings

Death: During the current reporting interval (25 February 2023 to 24 February 2024), a total of 3 fatal cases were retrieved. Of these cases, 1 case reported fatal EOI.

A CIOMS II LL of the fatal cases is presented in Appendix 7.15.1. Additional information on the fatal cases can also be found in Appendix 7.26, Death.

Booster: A cumulative CIOMS II LL of cases reported as booster is presented in Appendix 7.15.2.

Conclusion

Based on the evaluation of the cases and review of safety data from other sources, the information is consistent with what is currently known about thrombocytopenia, including immune thrombocytopenia.

16.3.2. New Information on Important Potential Risks

16.3.2.1. Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD)

Introduction

According to the cRMP (version 6.0; dated 25 October 2022) and EU-RMP (version 5.3; dated 13 February 2023), 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 interval 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 this reporting interval.

Cumulatively, 1 medically confirmed, post-marketing, primary dose case reporting VAED, including VAERD was retrieved. This case reported 1 serious EOI of antibody-dependent enhancement, and the outcome was not reported.

Booster Dose

There were no initial cases reported as booster, which were identified from the search of the Company global safety database during this reporting interval. In addition, cumulatively, there were no cases reported as booster.

Clinical Trial Cases

No cases were retrieved from either the Janssen-Sponsored Clinical or Janssen-Supported Clinical Studies.

Literature ICSR

No ICSR literature cases were received during the current reporting interval.

Line Listings

Death: During the current reporting interval (25 February 2023 to 24 February 2024), no fatal cases were retrieved.

Conclusion

Based on the evaluation of the case, and review of safety information from other sources, no new information was received on the topic of VAED, including VAERD.

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

In the FAR, the PRAC Rapporteur for the Ad26.COV2.S PBRER dated 25 February 2022 to 24 August 2022, circulated on 14 April 2023 (PRAC AR 2023) (procedure number: EMEA/H/C/PSUSA/00010916/202208), the PRAC Rapporteur indicated that,

"The section 'Update on special patient populations', ie pregnancy/breastfeeding; 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 should only be included and discussed in the PSUR if the reporting pattern changes and/or there is a safety issue/signal".

These sections will not be included within this PBRER and future PBRERs unless the reporting pattern changes and/or there is a safety issue/signal. Separate subsections are found in the Appendices below for those markets requiring this information.

16.3.5.1. Use During Pregnancy

Information on this topic is found in Appendix 7.16.

16.3.5.2. Use in breastfeeding women

Information on use in breastfeeding women is found in Appendix 7.16.

16.3.5.3. Use in immunocompromised patients

Information on this topic is found in Appendix 7.17.

16.3.5.4. Use in patients with autoimmune or inflammatory disorders

Information on this topic is found in Appendix 7.18.

16.3.5.5. Use in frail patients with comorbidities (eg, chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders)

Information on this topic is found in Appendix 7.19.

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

Information on this topic is found in Appendix 7.20.

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, 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 real world data analysis (RWDA) is to assess the potential association between the occurrence of predefined adverse events of special interest (AESI) and vaccination with the Ad26.COV2.S. Information on these analyses are found in Appendices 6.3.

16.3.6.1. Cardiac Disorders

16.3.6.1.1. Cardiomyopathy

Introduction

Cardiomyopathy is listed as an AESI in the cRMP, EU-RMP, and the United States Pharmacovigilance Plan (US PVP).

Methods

The Company global safety database was searched for medically confirmed and medically unconfirmed cases received during this reporting interval and cumulatively, coded to the search criteria provided in Appendix 5.

An Observed versus Expected (O/E) analysis has been performed and information is presented in the O/E Analysis subsection below.

Results/Discussion

During this reporting interval, a total of 4 (3 medically confirmed and 1 medically unconfirmed) initial, primary dose cases reporting cardiomyopathy were retrieved. Of these 4 cases, 3 were serious and 1 was nonserious reporting a total of 4 EOIs (3 serious, 1 nonserious).

During this reporting interval, no case reported as booster was identified.

Post-marketing Sources (Including Spontaneous and Solicited) Cases

Primary Dose

During this reporting interval, a total of 3 (2 medically confirmed and 1 medically unconfirmed) post-marketing, initial, primary dose cases reporting cardiomyopathy were retrieved. Of these 3 cases, 2 were serious and 1 was nonserious reporting 2 serious and 1 nonserious EOIs.

These 3 post-marketing, primary dose cases retrieved were reported from the US (n=2) and Belgium (n=1). These cases concerned females, aged 69 and 76 years, and 1 case reported age group as adult.

The EOIs included cardiomyopathy, cardiac hypertrophy, and ischaemic cardiomyopathy (n=1 each). Where reported, the TTO was 2 days and 735 days. The reported outcomes of the EOIs were resolved and not resolved (n=1 each).

Cumulatively, 77 (49 medically confirmed and 28 medically unconfirmed) post-marketing, primary dose cases reporting cardiomyopathy were retrieved. Of these 77 cases, 76 were serious and 1 was nonserious reporting a total of 86 EOIs (82 serious, 4 nonserious).

Booster Dose

During this reporting interval, no post-marketing, initial case reported as booster was identified.

Cumulatively, 5 (1 medically confirmed and 4 medically unconfirmed) cases reported as booster were identified. All cases were serious and reported a total of 5 serious EOIs. Of these cases, 4 were heterologous and 1 was homologous.

Clinical Trial Cases

During this reporting interval, 1 clinical case (primary dose and no booster) was retrieved from Janssen-sponsored clinical trials and no cases were retrieved from Janssen-supported clinical studies.

Janssen-sponsored Clinical Studies

During this reporting interval, 1 primary dose case reporting cardiomyopathy was retrieved from a Janssen-sponsored clinical study (VAC31518COV3009). This case concerned a 65-year-old male from [redacted] who developed a serious EOI of dilated cardiomyopathy 682 days after receiving Ad26.COV2.S vaccine. The outcome of the EOI was reported as not resolved.

During this reporting interval, no cases reported as booster were retrieved from Janssen-sponsored clinical studies.

Literature ICSR

No ICSR literature cases were received during the current reporting interval.

Line Listings

Death: During the current reporting interval (25 February 2023 to 24 February 2024), no fatal cases were retrieved.

Booster: A cumulative CIOMS II LL of cases reported as booster is presented in Appendix 7.21.

O/E Analysis Results

Appendix 6.1 contains the methods used to calculate and perform the O/E analyses for cardiomyopathy. Results of the restricted O/E and sensitivity analysis are presented in Table 64.

Table 64: Cardiomyopathy: Restricted O/E and Sensitivity Analysis Results (Cumulative Through 24 February 2024)

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	15.00	3.34	(1.87, 5.51)	6.86	(3.84, 11.32)
	≥60	10.00	0.77	(0.37, 1.41)	2.59	(1.24, 4.76)
EU	18 to 59	7.00	1.36	(0.55, 2.80)	2.79	(1.12, 5.74)
	≥60	5.00	0.49	(0.16, 1.14)	1.65	(0.54, 3.85)

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. Of these, 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 an O/E ratio of >1 for both age groups. Of these, the O/E ratio was statistically significant above 1 (lower bound of 95% confidence interval >1) for the 18 to 59 age group.

Full US and EU O/E analysis broad and restricted results (to include cumulative exposure, expected counts, background incidence rates) are provided in Appendix 6.2.

Discussion

Of the 4 primary dose cases received in this interval, majority of the cases concerned females. Ages reported ranged from 65 to 76 years. Two of the cases reported concurrent conditions that confound assessment, and these concurrent conditions included coronary artery disease, hypertension, obesity, and history of smoking (total exposure: 42 packs per year). The TTO ranged from 2 days to 735 days. No literature articles were identified during the interval. Overall, no specific patterns among cases reporting cardiomyopathy were identified.

Conclusion

Based on the evaluation of the cases and review of safety from other sources, the information is consistent with previous observations regarding cardiomyopathy following Ad26.COV2.S. No

safety concern has been identified; however, based on continued increased O/E results, the Company will continue to monitor cases of cardiomyopathy as an AESI.

16.3.6.2. Nervous System Disorders

16.3.6.2.1. Encephalitis, Including Acute Disseminated Encephalomyelitis (ADEM) and Meningoencephalitis

Introduction

Encephalitis, including acute disseminated encephalomyelitis (ADEM) and meningoencephalitis, is listed as an AESI in the cRMP, EU-RMP, and the US PVP. A cumulative review of encephalitis, including ADEM through 24 August 2023 is presented in Appendix 7.10. For this section, the interval review concerned cases from 25 August 2023 to 24 February 2024.

Methods

The Company global safety database was searched for medically confirmed and medically unconfirmed cases received during this reporting interval 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

During this reporting interval, a total of 6 medically confirmed (no medically unconfirmed) initial, primary dose cases reporting encephalitis, including ADEM and meningoencephalitis, were retrieved. All these 6 cases were serious and reported a total of 9 EOI (all serious).

During this reporting interval, no initial cases reported as booster dose were identified.

Post-marketing Sources (Including Spontaneous and Solicited) Cases

Primary Dose

During this reporting interval, a total of 6 (all medically confirmed) post-marketing sources, (including spontaneous and solicited), initial, primary dose cases reporting encephalitis, including ADEM and meningoencephalitis were retrieved. All cases were assessed as serious which reported a total of 9 EOI (all serious).

Cumulatively, 100 (69 medically confirmed and 31 medically unconfirmed) post-marketing, primary dose cases reporting encephalitis, including ADEM and meningoencephalitis were retrieved. All cases were serious and reported a total of 107 serious EOI.

An overview of these cases is presented in Table 65.

Table 65: Characteristics of Post-marketing Cases Involving the Use of Ad26.COV2.S and Reporting Encephalitis, Including ADEM and Meningoencephalitis

Case Characteristics		Number of Cases Received During the Reporting Interval=6	Number of Cases Received Cumulatively=100[a]
Sex	Female	1	43
	Male	2	49
	NR	3	8
Age (Years)[b]	18 to 35	1	26
Minimum: 33	51 to 64	1	8
Maximum:89	≥65	1	9
Mean: 60.7	Adult	1	2
Median: 60	NR	2	8
Sources	Spontaneous	3	97
	Clinical study (noninterventional, solicited)	3	3
Country/Territory	United States	3	27
	Portugal	1	1
	Romania	1	3
	South Africa	1	3
Event Characteristics		**Number of Events of Interest=9**	**Number of Events of Interest=107**
Seriousness (Event Level)[c]	Serious	9	107
Outcome (Event Level)[c]	Not resolved	3	32
	Resolving	2	10
	Resolved	1	11
	NR	3	45

Key: ADEM=Acute Disseminated Encephalomyelitis and Meningoencephalitis; EOI=Event(s) of Interest; NR=Not Reported

a: For the cumulative column, the counts were presented in decreasing order based on the current reporting interval (25 February 2023 to 24 February 2024).

b: The median and mean age calculation were based on the current reporting interval (25 February 2023 to 24 February 2024). Age group was presented for cases where age was not reported.

c: Seriousness and outcome have been presented for the EOI. A single case may report more than 1 EOI.

Of these 6 post-marketing, primary dose cases received, the reported countries/territories of origin were the US (n=3), and Portugal, Romania, and South Africa (n=1 each). These cases concerned 2 males, 1 female, and 3 cases did not report sex. The age range was from 33 to 89 years.

The frequency distribution of the MedDRA PTs of interest reported is presented in Table 66.

Table 66: Frequency Distribution 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 Reporting Interval[a]		Number of Events Reported Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
Encephalitis	6	0	48	0
Acute disseminated encephalomyelitis	1	0	23	0
Encephalitis autoimmune	1	0	8	0
Encephalomyelitis	1	0	11	0

Key: ADEM=Acute Disseminated Encephalomyelitis; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: A single case may report more than 1 MedDRA PT.
b: For the cumulative column, the events were presented in decreasing order based on the event counts of the current reporting interval (25 February 2023 to 24 February 2024).

The EOI reported at a frequency (≥6) included encephalitis (n=6). The TTO in 1 case was the same day and was not reported for remaining 5 cases. Of the 9 EOI, outcomes were reported for 6 and are as follows: not resolved (n=3), resolving (n=2) and resolved (n=1).

Booster Dose

During this reporting interval, no post-marketing, initial cases reported as booster were identified.

Cumulatively, 3 (2 medically confirmed and 1 medically unconfirmed) cases reported as booster were identified. All cases were serious and reported a total of 3 serious EOI. Of these cases, 2 were homologous and 1 was heterologous.

Clinical Trial Cases

During this reporting interval, no cases were retrieved from either the Janssen-sponsored clinical or Janssen-supported clinical studies.

Literature ICSR

ICSR literature cases received during the current reporting interval were reviewed, and no information was identified that would change the information known about encephalitis, including ADEM and meningoencephalitis.

Line Listings

Death: During the current reporting interval (25 February 2023 to 24 February 2024), 1 fatal case was retrieved. This case did not report fatal EOI.

A CIOMS II LL of the fatal cases is presented in Appendix 7.22.1. Additional information on the fatal cases can also be found in Appendix 7.26, Death.

Booster: A cumulative CIOMS II LL of cases reported as booster is presented in Appendix 7.22.2.

O/E Analysis Results

Results of the restricted O/E and sensitivity analysis for encephalitis and acute disseminated encephalomyelitis (ADEM) are presented in Table 67. Appendix 6.1 contains the methodology used to calculate and perform the O/E analyses for the AESI.

Table 67: Encephalitis, ADEM alone: Restricted O/E and Sensitivity Analysis Results (Cumulative Through 24 February 2024)

		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	14.29	0.11	(0.06, 0.19)	1.97	(1.09, 3.29)
		≥60	3.69	0.04	(0.01, 0.11)	0.64	(0.16, 1.71)
	EU	18 to 59	24.00	0.17	(0.11, 0.25)	2.88	(1.85, 4.29)
ADEM	**US**	18 to 59	7.64	0.61	(0.26, 1.21)	3.16	(1.33, 6.31)
		≥60	0.35	0.2	(0.00, 2.56)	1.02	(0.00, 12.79)
	EU	18 to 59	8.00	0.55	(0.24, 1.09)	2.88	(1.24, 5.67)

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; W/O=Without

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 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).

Full US and EU O/E analysis broad and restricted results (to include cumulative exposure, expected counts, background incidence rates) are provided in Appendix 6.2.

ADEM

The US restricted sensitivity analysis showed an O/E ratio of >1 for both age groups. The lower bound of the confidence interval for the male ≥60 age group was <1 in the previous interval. Of these, the O/E ratio was statistically significant above 1 (lower bound of 95% confidence interval >1) for the 18 to 59 age group. The EU 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 lower bound of the confidence interval for the 18 to 59 age group was <1 in the previous interval.

Full US and EU O/E analysis broad and restricted results (to include cumulative exposure, expected counts, background incidence rates) are provided in Appendix 6.2.

Conclusion

Based on the evaluation of the cases, and review of safety data from other sources, the information retrieved during the reporting interval remains consistent with previous observations regarding

encephalitis, including ADEM and meningoencephalitis following Ad26.COV2.S. No safety concern has been identified; however, based on the elevated O/E ratio, and previously confirmed signals for other neuroinflammatory and demyelinating conditions (GBS and TM), the Company will continue to closely monitor cases of encephalitis, including ADEM and meningoencephalitis as an AESI.

16.3.6.2.2. 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 interval 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

During this reporting interval, a total of 8 (4 medically confirmed and 4 medically unconfirmed) initial, primary dose cases reporting multiple sclerosis, including optic neuritis, were retrieved. All 8 cases were serious and reported a total of 10 serious EOIs.

During this reporting interval, a total of 2 medically unconfirmed and no medically confirmed initial cases reported as booster were identified. These 2 cases were serious and reported a total of 2 serious EOIs reporting multiple sclerosis, including optic neuritis. These 2 cases were reported for heterologous booster.

Post-marketing Source (including spontaneous and solicited) Cases

Primary Dose

During this reporting interval, a total of 8 (4 medically confirmed and 4 medically unconfirmed) post-marketing, initial, primary dose cases reporting multiple sclerosis, including optic neuritis, were retrieved. All 8 cases were serious and reported a total of 10 serious EOIs.

Cumulatively, 82 (40 medically confirmed and 42 medically unconfirmed) post-marketing, primary dose cases reporting multiple sclerosis, including optic neuritis, were retrieved. All 82 cases were serious and reported a total of 86 serious EOIs.

An overview of these cases is presented in Table 68.

Table 68: 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 Reporting Interval=8	Number of Cases Received Cumulatively=82[a]
Sex	Male	4	35
	Female	1	40
	NR	3	7
Age (Years)[b]	18 to 35	2	21
Minimum: 32	36 to 50	2	34
Maximum: 60	51 to 64	1	14
Mean: 41.6	NR	3	9
Median: 37			
Source	Spontaneous	5	78
	Clinical study (noninterventional; solicited)	3	4
Country/Territory	United States	3	44
	Czech Republic	1	4
	Germany	1	11
	Poland	1	3
	Slovak Republic	1	1
	Zambia	1	1
Event Characteristics		**Number of Events=10**	**Number of Events=86**
Seriousness (Event Level)[c]	Serious	10	86
Outcome (Event Level)[c]	Not resolved	2	51
	Resolved	1	6
	Resolving	1	6
	NR	6	18

Key: EOI=Event(s) of Interest; NR=Not Reported

a: For the cumulative column, the counts were presented in decreasing order based on the current reporting interval (25 February 2023 to 24 February 2024).

b: The median and mean age calculation were based on the current reporting interval (25 February 2023 to 24 February 2024).

c: Seriousness and outcome have been presented for the EOI.

Of these 8 post-marketing primary dose cases received, the countries/territories of origin were the US (n=3), followed by Czech Republic, Germany, Poland, Slovak Republic, and Zambia (n=1 each). These cases concerned 4 males, 1 female, and 3 that did not report sex. The age range was from 32 to 60 years.

The frequency distribution of the MedDRA PTs of interest reported is presented in Table 69.

Table 69: Frequency Distribution 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 Events Reported During the Interval Reporting interval[a]		Number of Events Reported Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
Multiple sclerosis	5	0	40	0
Optic neuritis	3	0	30	0
Multiple sclerosis relapse	1	0	13	0
Relapsing multiple sclerosis	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 interval (25 February 2023 to 24 February 2024).
b: For the cumulative column, the events were presented in decreasing order based on the event counts of the current reporting interval (25 February 2023 to 24 February 2024).

The EOIs included multiple sclerosis (n=5), optic neuritis (n=3), multiple sclerosis relapse, and relapsing multiple sclerosis (n=1 each). The mean and median TTO was 47 days, and the range was from 44 to 50 days. Where reported (n=4), the outcomes were not resolved (n=2), resolved, and resolving (n=1 each).

Booster Dose

During this reporting interval, a total of 2 medically unconfirmed post-marketing, initial cases reported as booster were identified. These 2 cases were serious and reported a total of 2 serious EOIs. These 2 cases were heterologous.

Cumulatively, 10 (4 medically confirmed and 6 medically unconfirmed) post-marketing cases reported as booster were identified. All 10 cases were serious and reported a total of 12 serious EOIs. Of these cases, 7 were heterologous and 3 were homologous.

In these 2 initial post-marketing cases reported as booster, the countries/territories of origin were the US and Italy (n=1 each). Both cases were reported for males. Of these 2 cases, 1 reported the age as 49 years, and the age was not reported in another case. The TTO was reported as 1 day in 1 case and not reported in another. The outcome was reported as not resolved in 1 and was not reported in another case.

Clinical Trial Cases

During this reporting interval, no cases were retrieved from Janssen-sponsored and Janssen-supported clinical studies.

Literature ICSR

ICSR literature cases received during the current reporting interval were reviewed, and no information was identified that would change the information known about multiple sclerosis, including optic neuritis.

Line Listings

Death: During the current reporting interval (25 February 2023 to 24 February 2024), 2 fatal cases were retrieved. However, none of these cases reported fatal EOIs.

A CIOMS II LL of the fatal cases is presented in Appendix 7.23.1. Additional information on the fatal cases can also be found in Appendix 7.26, Death.

Booster: A cumulative CIOMS II LL of cases reported as booster is presented in Appendix 7.23.2.

O/E Analysis Results

Appendix 6.1 contains the methodology used to calculate and perform the O/E analyses for the AESI.

Since the previous PBRER DLD (24 February 2023), 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.

Full O/E analysis broad results (to include cumulative exposure, expected counts, background incidence rates) are provided in Appendix 6.2.

Conclusion

Based on the evaluation of the cases and review of safety data from other sources, the information is consistent with what is currently known about multiple sclerosis, including optic neuritis.

16.3.6.2.3. Narcolepsy

Introduction

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

In the second updated PRAC Rapporteur AR (PRAC AR 2023; procedure number EMEA/H/C/PSUSA/00010916/202208) for the Ad26.COV2.S PBRER dated 25 February 2022 to 24 August 2022, circulated on 04 April 2023, the rapporteur concluded that the Company should 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 interval and cumulatively, 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

During this reporting interval, a total of 25 (4 medically confirmed and 21 medically unconfirmed) initial, primary dose cases reporting narcolepsy were retrieved. There were 14 serious and 11 nonserious cases which reported a total of 25 EOIs (8 serious, 17 nonserious).

During this reporting interval, a total of 4 (1 medically confirmed and 3 medically unconfirmed) initial cases reported as booster dose were identified. There were 2 serious and 2 nonserious cases which reported a total of 4 nonserious EOIs. All these 4 cases were heterologous.

Post-marketing Sources (Including Spontaneous and Solicited) Cases

Primary Dose

During this reporting interval, a total of 25 (4 medically confirmed and 21 medically unconfirmed) post-marketing source (including spontaneous and solicited), initial, primary dose cases reporting narcolepsy were retrieved. There were 14 serious and 11 nonserious cases which reported a total of 25 EOIs (8 serious, 17 nonserious).

Cumulatively, 611 (84 medically confirmed and 527 medically unconfirmed) post-marketing, primary dose cases reporting narcolepsy were retrieved. There were 205 serious and 406 nonserious cases which reported a total of 619 EOIs (101 serious, 518 nonserious).

An overview of these cases is presented in Table 70.

Table 70: Characteristics of Post-marketing Cases Involving the Use of Ad26.COV2.S and Reporting Narcolepsy

Case Characteristics		Number of Cases Received During the Reporting interval=25	Number of Cases Received Cumulatively=611[a]
Sex	Female	15	308
	Male	9	254
	NR	1	49
Age (Years)[b] **Minimum: 21** **Maximum:71** **Mean: 45.9** **Median: 47**	18 to 35	4	133
	36 to 50	12	153
	51 to 64	5	158
	≥65	2	70
	Adult	2	8
	NR	0	89
Sources	Spontaneous	23	579
	Clinical study (noninterventional, solicited)	2	32
Country/Territory	Germany	16	156
	Netherlands	3	17
	Spain	2	11
	United States	2	305
	Poland	1	18
	Switzerland	1	8

Table 70: Characteristics of Post-marketing Cases Involving the Use of Ad26.COV2.S and Reporting Narcolepsy

Event Characteristics		Number of Events=25	Number of Events=619
Seriousness (Event Level)[c]	Nonserious	17	518
	Serious	8	101
Outcome (Event Level)[c]	Not resolved	13	222
	Resolved	3	124
	Resolved with sequelae	3	14
	Resolving	2	70
	Fatal	0	1
	NR	4	188

Key: EOI=Event(s) of Interest; NR=Not Reported
a: For the cumulative column, the counts were presented in decreasing order based on the current reporting interval (25 February 2023 to 24 February 2024).
b: The median and mean age calculation were based on the current reporting interval (25 February 2023 to 24 February 2024). Age group was presented for cases where age was not reported.
c: Seriousness and outcome have been presented for the EOI. A single case may report more than 1 EOI.

Of these 25 post-marketing, primary dose cases received, the most frequently reported countries/territories of origin were Germany (n=16), followed by the Netherlands (n=3). These cases concerned 15 females, 9 males, and 1 case that did not report sex. The age range was from 21 to 71 years.

The frequency distribution of the MedDRA PTs of interest reported is presented in Table 71.

Table 71: Frequency Distribution 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 Reporting Interval[a]		Number of Events Reported Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
Sleep disorder	6	15	76	299
Hypersomnia	1	2	20	219
Narcolepsy	1	0	4	0

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: The MedDRA PTs of interest sorted by decreasing order for the reporting interval (25 February 2023 to 24 February 2024). A single case may report more than 1 MedDRA PT.
b: For the cumulative column, the events were presented in decreasing order based on the event counts of the current reporting interval (25 February 2023 to 24 February 2024).

The EOIs included sleep disorder (n=21), hypersomnia (n=3), and narcolepsy (n=1). The mean and median TTO were 51.1 and 9.5 days, respectively, and the range was from 0 to 242 days. Of the 25 EOIs, outcomes were reported for 21 and are as follows: not resolved (n=13), resolved, resolved with sequelae (n=3 each), and resolving (n=2).

Booster Dose

During this reporting interval, a total of 4 (1 medically confirmed and 3 medically unconfirmed) cases reported as booster dose were identified. There were 2 serious and 2 nonserious cases which reported a total of 4 nonserious EOIs. All these 4 cases were heterologous.

Cumulatively, 53 (6 medically confirmed and 47 medically unconfirmed) cases reported as booster were retrieved. There were 18 serious and 35 nonserious cases which reported a total of 54 EOIs (7 serious; 47 nonserious). Of these cases, 33 were heterologous and 20 were homologous.

An overview of these cases is presented in Table 72.

Table 72: 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 Reporting Interval=4	Number of Cases Received Cumulatively=53[a]
Sex	Female	2	31
	Male	2	18
Age (Years)[b]	18 to 35	1	11
Minimum: 29	36 to 50	1	18
Maximum:56	51 to 64	2	15
Mean: 43.5			
Median: 44.5			
Sources	Spontaneous	2	41
	Clinical study (noninterventional, solicited)	2	12
Country/Territory	Germany	4	24
Classification	Heterologous	4	33
Event Characteristics		**Number of Events=4**	**Number of Events=54**
Seriousness (Event Level)[c]	Nonserious	4	47
Outcome (Event Level)[c]	Resolved	1	9
	Resolving	1	8
	Not resolved	1	18
	NR	1	15

Key: NR=Not Reported

a: For the cumulative column, the counts were presented in decreasing order based on the current reporting interval (25 February 2023 to 24 February 2024).

b: The median and mean age calculations were based on the current reporting interval (25 February 2023 to 24 February 2024).

c: Seriousness and outcome have been presented for the events of interest. A single case may report more than 1 event of interest.

All these 4 post-marketing cases reported as booster were reported from Germany (n=4). These cases concerned 2 males and 2 females. The age range was from 29 to 56 years.

The frequency distribution of the MedDRA PTs of interest reported in post-marketing cases reported as booster is presented in Table 73.

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

MedDRA PTs	Number of Events Reported During the Reporting Interval[a]		Number of Events Reported Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
Sleep disorder	0	4	5	34

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: A single case may report more than 1 MedDRA PT.
b: For the cumulative column, the events were presented in decreasing order based on the event counts of the current reporting interval (25 February 2023 to 24 February 2024).

The EOIs included sleep disorder (n=4). The mean and median TTO were 149.7 and 164 days, respectively, and the range is from 0 to 285 days. Of the 4 EOIs, the outcomes were reported for 3 and are as follows: resolved, resolving, and not resolved (n=1 each).

Clinical Trial Cases

During this reporting interval, there were no cases were retrieved from either the Janssen-Sponsored Clinical or Janssen-Supported Clinical Studies.

Literature ICSR

ICSR literature case received during the reporting interval was reviewed, and no new information was identified that would change the information known about the AESI narcolepsy.

Line Listings

Death: During the current reporting interval (25 February 2023 to 24 February 2024), no fatal cases were retrieved.

Booster: A cumulative CIOMS II LL of cases reported as booster is presented in Appendix 7.24.

O/E Analysis Results

Results of the restricted O/E and sensitivity analysis are presented in Table 74. Appendix 6.1 contains the methodology used to calculate and perform the O/E analyses for the AESI.

Table 74: Narcolepsy: Restricted O/E Analysis with Sensitivity Analysis Results (Cumulative Through 24 February 2023)

	Restricted O/E Analysis				Sensitivity Analysis	
Region	Age Range (Years)	Observed Counta	O/E Ratio (95% CI)b (PE, 100% RP)		O/E Ratio (95% CI)b (LB, 50% RP)	
EU	18 to 59	113.33	0.89	(0.73, 1.07)	3.41	(2.81, 4.10)
	≥60	23.63	3.24	(2.07, 4.84)	27.38	(17.47, 40.86)

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.

a: Counts included EOI (from valid cases) that occurred within the risk window (Day: 1 to 180) only.

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

The EU 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).

Full US and EU O/E analysis broad and restricted results (to include cumulative exposure, expected counts, background incidence rates) are provided in Appendix 6.2.

Conclusion

Based on the evaluation of the cases and review of safety data from other sources, the information retrieved during the reporting interval remains consistent with previous observations regarding narcolepsy following Ad26.COV2.S. No safety concern has been identified; however, based on previously confirmed signals for other neuroinflammatory and demyelinating conditions (GBS and TM) and the long latency of the disease, the Company will continue to closely monitor narcolepsy as an AESI.

16.3.6.3. Vascular Disorders

16.3.6.3.1. Cerebrovascular Events

Introduction

Cerebrovascular events are listed as an AESI in the cRMP, EU-RMP, and US PVP. The Company opened a signal on haemorrhagic cerebrovascular events- based on disproportionate reporting in WHO's VigiBase. The Company will provide the outcome of this evaluation in the next scheduled PBRER.

Methods

The Company global safety database was searched for medically confirmed and medically unconfirmed cases received during this reporting interval and cumulatively, 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

During this reporting interval, a total of 42 (20 medically confirmed and 22 medically unconfirmed) initial, primary dose cases reporting cerebrovascular events were retrieved. All these serious cases reported a total of 51 EOIs (all serious).

During this reporting interval, a total of 11 (4 medically confirmed and 7 medically unconfirmed) initial cases reported as booster were identified. All these serious cases reported a total of 13 EOIs (all serious). Of these cases, 7 were homologous and 4 were heterologous.

Post-marketing Source (including spontaneous and solicited) Cases

Primary Dose

During this reporting interval, a total of 42 (20 medically confirmed and 22 medically unconfirmed) post-marketing source (including spontaneous and solicited), initial, primary dose cases reporting cerebrovascular events were retrieved. All these serious cases reported a total of 51 EOIs (all serious).

Cumulatively, 1,671 (963 medically confirmed and 708 medically unconfirmed) post-marketing, primary dose cases reporting cerebrovascular events were retrieved. There were 1,669 serious and 2 nonserious cases which reported a total of 2,294 EOIs (2,290 serious; 4 nonserious).

An overview of these cases is presented in Table 75.

Table 75: Characteristics of Post-marketing Cases Involving the Use of Ad26.COV2.S and Reporting Cerebrovascular Events

Case Characteristics		Number of Cases Received During the Reporting Interval=42	Number of Cases Received Cumulatively=1,671[a]
Sex	Female	20	857
	Male	19	740
	NR	3	74
Age (Years)[b]	18 to 35	6	187
Minimum: 20	36 to 50	6	380
Maximum:88	51 to 64	15	508
Mean: 53.7		8	423
Median: 57	≥65		
	NR	7	159
Sources	Spontaneous	41	1,647
	Clinical study (noninterventional, solicited)	1	24
Country/Territory	United States	18	1,116
	Germany	9	172
	South Africa	6	25
	Italy	2	46
	Romania	2	7
	Colombia	1	6
	Croatia	1	1

Table 75: Characteristics of Post-marketing Cases Involving the Use of Ad26.COV2.S and Reporting Cerebrovascular Events

Case Characteristics		Number of Cases Received During the Reporting Interval=42	Number of Cases Received Cumulatively=1,671[a]
	Malaysia	1	1
	Netherlands	1	45
	Slovenia	1	6
Event Characteristics		**Number of Events=51**	**Number of Events=2,294**
Seriousness (Event Level)[c]	Serious	51	2,290
Outcome (Event Level)[c]	Not resolved	19	867
	Resolving	7	223
	Resolved with sequelae	5	44
	Fatal	1	219
	Resolved	1	280
	Unknown	18	661

Key: EOI=Event(s) of Interest; NR=Not Reported
a: For the cumulative column, the counts were presented in decreasing order based on the current reporting interval (25 February 2023 to 24 February 2024).
b: The median and mean age calculation were based on the current reporting interval (25 February 2023 to 24 February 2024).
c: Seriousness and outcome have been presented for the EOI. A single case may report more than 1 EOI.

Of these 42 post-marketing, primary dose cases received, the most frequently reported countries/territories of origin (n>2) were the US (n=18), followed by Germany (n=9) and South Africa (n=6). These cases concerned 20 females, 19 males, and 3 cases that did not report sex. The age range was from 20 to 88 years.

The frequency distribution of the MedDRA PTs of interest reported is presented in Table 76.

Table 76: Frequency Distribution 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 Serious Events Reported During the Reporting Interval[a]	Number of Serious Events Reported Cumulatively[b]
Cerebrovascular accident	22	686
Cerebral infarction	5	111
Transient ischaemic attack	5	142
Carotid artery thrombosis	2	19
Cerebral haemorrhage	2	110
Cerebral ischaemia	2	13
Ischaemic stroke	2	117

Table 76: Frequency Distribution of MedDRA PTs of Interest in Post-marketing Primary dose Cases Reporting Cerebrovascular Events With the Use of Ad26.COV2.S

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 interval (25 February 2023 to 24 February 2024). A single case may report more than 1 MedDRA PT.
b: For the cumulative column, the events were presented in decreasing order based on the event counts of the current reporting interval (25 February 2023 to 24 February 2024).

The EOIs reported at a frequency >2 included cerebrovascular accident (n=22), cerebral infarction (n=5), and transient ischaemic attack (n=5). The mean and median TTO were 59 and 154.5 days, respectively, and the range was from 0 to 712 days. Of the 51 EOIs, outcomes were reported for 33 as follows: not resolved (n=19), resolving (n=7), resolved with sequelae (n=5), resolved, and fatal (n=1 each).

Information on Patients ≤40 Years of Age (including fatalities)

During this reporting interval, 1 fatal (primary dose) case was reported in patients ≤40 years of age. In addition, a total of 8 non-fatal (7 primary dose and 1 case reported as booster) cases were reported in patients ≤40 years of age. Case information for these cases which occurred in patients ≤40 years of age are included in Appendix 7.25.

One case involved a fatal non-haemorrhagic event (primary dose). A TTO was not reported for that fatal case. The case did not report concomitant medications, diagnostic test results and/or concurrent disease that would confound the case, and reported clean medical history.

Of the 8 non-fatal cases, the EOI was outside the 28-day risk window in 4 cases (all primary dose). Of the remaining 4 cases, assessment in 1case (reported as booster) was confounded by the patients' concurrent disease (obesity). Of the remaining 3 cases (all primary dose cases) lacked relevant details, including TTO, medical history, concomitant medications, and diagnostic test results. Case information for the 8 non-fatal cases that occurred in patients ≤40 years of age are included in Appendix 7.25.

Review of the cases, including demographics, concomitant medications, concurrent conditions/medical history, outcome, and seriousness received during this reporting interval did not identify evidence suggestive of cerebrovascular events being causally associated with Ad26.COV2.S.

Booster Dose

During this reporting interval, a total of 11 (4 medically confirmed and 7 medically unconfirmed) cases reported as booster were identified. All these serious cases reported a total of 13 events (all serious). Of these cases, 4 were heterologous and 7 were homologous.

Cumulatively, 79 (41 medically confirmed and 38 medically unconfirmed) cases reported as booster were retrieved. There were 78 cases serious and 1 nonserious case which reported a total

of 106 EOIs (104 serious; 2 nonserious). Of these cases, 26 were heterologous and 53 were homologous.

An overview of these cases is presented in Table 77.

Table 77: 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 Reporting Interval=11	Number of Cases Received Cumulatively =79[a]
Sex	Male	8	44
	Female	1	30
	NR	2	5
Age (Years)[b] **Minimum: 36** **Maximum:93** **Mean: 60.7** **Median: 59**	36 to 50	1	16
	51 to 64	5	27
	≥65	2	16
	NR	3	13
Sources	Spontaneous	10	74
	Clinical study (solicited, noninterventional)	1	3
Country/Territory	United States	5	45
	Germany	3	14
	Netherlands	1	1
	Slovenia	1	1
	Switzerland	1	1
Classification	Heterologous	4	26
	Homologous	7	53
Event Characteristics		**Number of Events=13**	**Number of Events=106**
Seriousness (Event Level)[c]	Serious	13	104
Outcome (Event Level)[c]	Not resolved	3	19
	Resolving	1	8
	Fatal	1	16
	Resolved	1	15
	NR	7	44

Key: EOI=Event(s) of Interest; NR=Not Reported; US=United States

a: For the cumulative column, the counts were presented in decreasing order based on the current reporting interval (25 February 2023 to 24 February 2024).

b: The median and mean age calculations were based on the current reporting interval (25 February 2023 to 24 February 2024). Age group was presented for cases where age was not reported.

c: Seriousness and outcome have been presented for the EOI. A single case may report more than 1 EOI.

Among these 11 post-marketing cases reported as booster, the reported country/territory of origin (>1) was US (n=5), followed by Germany (n=3). These cases concerned 8 males, 1 female, and 2 cases that did not report sex. The age range was from 36 to 93 years.

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

Table 78: Frequency Distribution 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 Reporting Interval[a]	Number of Serious Events Reported Cumulatively[b]
Cerebrovascular accident	6	38
Ischaemic stroke	2	7
Transient ischaemic attack	2	9
Cerebral haemorrhage	1	3
Lacunar stroke	1	2
Spinal cord infarction	1	1

Key: EOI=Event(s) of Interest; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term

a: The MedDRA PTs of interest are sorted by decreasing order for the current reporting interval (25 February 2023 to 24 February 2024). A single case may report more than 1 EOI.

b: For the cumulative column, the events were presented in decreasing order based on the event counts of the current reporting interval (25 February 2023 to 24 February 2024).

The EOIs at a frequency >1 included cerebrovascular accident (n=6), ischaemic stroke (n=2), and transient ischaemic attack (n=2). The mean and median TTO were 218.6 and 151 days, respectively, and the range was from 13 to 638 days. Of the 13 EOIs, the outcomes were reported for 6 as follows: not resolved (n=3), resolved, fatal, and resolving (n=1 each).

Clinical Trial Cases

No primary or booster cases were retrieved from either the Janssen-sponsored or Janssen-supported clinical studies.

Literature ICSR

ICSR literature cases received during the current reporting interval were reviewed, and no information was identified that would change the information known about cerebrovascular events.

Line Listings

Death: During the current reporting interval (25 February 2023 to 24 February 2024), a total of 5 fatal cases were retrieved. These 5 cases, reported 5 fatal cerebrovascular events.

A CIOMS II LL of the fatal cases is presented in Appendix 7.25.1. Additional information on the fatal cases can also be found in Appendix 7.26, Death.

Booster: A cumulative CIOMS II LL of cases reported as booster is presented in Appendix 7.25.2.

O/E Analysis Results

Cerebrovascular Events

Results of the restricted O/E and sensitivity analysis are presented in Table 79. Appendix 6.1 contains the methodology used to calculate and perform the O/E analyses for the AESI.

Table 79: Cerebrovascular Events - Haemorrhagic: Restricted O/E and Sensitivity Analysis Results (Cumulative Through 24 February 2024)

		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	9.45	0.35	(0.16, 0.66)	3.08	(1.44, 5.77)
		30 to 39	13.66	0.38	(0.20, 0.63)	4.87	(2.64, 8.22)
		40 to 49	32.73	0.69	(0.48, 0.98)	11.22	(7.71, 15.77)
		50 to 64	62.48	0.44	(0.33, 0.56)	7.15	(5.49, 9.16)
		65 to 74	35.24	0.3	(0.21, 0.42)	3.32	(2.32, 4.62)
		≥75	32.34	0.2	(0.14, 0.29)	2.54	(1.74, 3.58)
	Male	18 to 29	1.70	0.04	(0.00, 0.14)	0.28	(0.03, 1.12)
		30 to 39	9.77	0.16	(0.08, 0.31)	2	(0.95, 3.70)
		40 to 49	20.94	0.28	(0.18, 0.43)	4.58	(2.83, 7.01)
		50 to 64	64.03	0.3	(0.23, 0.38)	4.64	(3.57, 5.92)
		65 to 74	53.67	0.35	(0.26, 0.45)	3.15	(2.36, 4.11)
		≥75	24.38	0.18	(0.12, 0.27)	2.44	(1.57, 3.62)
EU	Female	18 to 29	5.27	2.06	(0.69, 4.71)	11.71	(3.95, 26.77)
		30 to 39	2.21	0.6	(0.08, 2.05)	2.52	(0.35, 8.62)
		40 to 49	11.77	1.21	(0.62, 2.13)	3.69	(1.89, 6.48)
		50 to 64	13.81	0.41	(0.22, 0.69)	1.09	(0.59, 1.83)
	Male	18 to 29	5.30	1.79	(0.60, 4.08)	9.34	(3.16, 21.30)
		30 to 39	7.23	0.89	(0.36, 1.81)	2.95	(1.21, 6.01)
		40 to 49	4.65	0.29	(0.09, 0.68)	0.79	(0.24, 1.89)

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 concerned except the 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 and 40 to 49 and male 18 to 29 and 30 to 39 age groups.

Full US and EU O/E analysis broad and restricted results (to include cumulative exposure, expected counts, background incidence rates) are provided in Appendix 6.2.

Cerebrovascular Events - Non-Haemorrhagic

Results of the restricted analysis with sensitivity analysis are presented in Table 80.

Table 80: Cerebrovascular Events – Non-Haemorrhagic: Restricted O/E and Sensitivity Analysis Results (Cumulative Through 24 February 2024)

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	10.66	0.28	(0.14, 0.51)	3.74	(1.84, 6.76)
		30 to 39	17.97	0.21	(0.12, 0.33)	4.32	(2.56, 6.83)
		40 to 49	42.06	0.32	(0.23, 0.43)	7.58	(5.46, 10.24)
		50 to 64	73.16	0.16	(0.12, 0.20)	4.59	(3.60, 5.77)
		65 to 74	39.54	0.1	(0.07, 0.13)	1.31	(0.94, 1.79)
		≥75	51.49	0.09	(0.07, 0.12)	1.15	(0.86, 1.51)
	Male	18 to 29	4.58	0.12	(0.04, 0.30)	1.34	(0.41, 3.25)
		30 to 39	13.63	0.12	(0.07, 0.21)	2.01	(1.09, 3.39)
		40 to 49	19.77	0.11	(0.07, 0.17)	1.98	(1.21, 3.07)
		50 to 64	86.67	0.13	(0.11, 0.17)	2.49	(1.99, 3.07)
		65 to 74	58.54	0.12	(0.09, 0.15)	1.31	(0.99, 1.69)
		≥75	26.31	0.06	(0.04, 0.09)	0.9	(0.59, 1.32)
EU	Female	18 to 29	6.27	0.67	(0.25, 1.44)	2.34	(0.88, 5.02)
		30 to 39	7.21	0.43	(0.18, 0.88)	1.21	(0.50, 2.48)
	Male	18 to 29	9.60	0.92	(0.43, 1.71)	3.14	(1.48, 5.84)
		30 to 39	13.46	0.8	(0.43, 1.36)	2.28	(1.23, 3.86)

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 to28) 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 ≥75 age groups. The lower bound of the confidence interval for the male 65 to 74 age group was <1 in the previous interval. 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 and 65 to 74 age groups.

The EU restricted sensitivity analysis showed an O/E ratio of >1 for both 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 both male age groups.

Full US and EU O/E analysis broad and restricted results (to include cumulative exposure, expected counts, background incidence rates) are provided in Appendix 6.2.

Conclusion

Based on the evaluation of the cases and review of safety data 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. Death

As per PRAC confirmation received in the PRAC FAR (PRAC AR 2022) for the Ad26.COV2.S PBRER (25 August 2021 to 24 February 2022) (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 this PBRER or in future PBRERs. However, a separate subsection is found in Appendix 7.26 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 53,288,029 (CDC [2022], ECDC [2022], KDCA [2022]), available clinical trial data, as well as RWE analyses (see Appendix 6.3). 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

Important risks identified during clinical studies or post-marketing experience of Ad26.COV2.S include:

The current cRMP (version 8.0; dated 06 February 2024) was used as a reference for this section. Immune thrombocytopenia re-classified as an important identified risk and renamed as Thrombocytopenia, including ITP. Myocarditis and pericarditis is listed as an IIR in the current cRMP.

Important risks identified during clinical studies or post-marketing experience of Ad26.COV2.S include:

Thrombosis With Thrombocytopenia Syndrome

Potential Mechanisms:

The exact mechanism of TTS following vaccination with Ad26.COV2.S is unknown. Several hypothetical biological mechanisms have been proposed to explain the pathophysiology of vaccine-induced TTS, including vaccine-mediated induction of platelet-activating antibodies directed against the cationic platelet chemokine PF4 (CXCL4), subsequently referred to as anti-PF4 antibodies (Greinacher 2021).

The Company assessed a possible interaction between PF4 and Ad26.COV2.S and does not have conclusive evidence for binding of Ad26.COV2.S to PF4 in vitro. Several research teams in the TTS field are pursuing to investigate the potential binding of different adenovirus vectors or other components in the formulation of the COVID-19 vaccines to PF4. The Company will continue to follow the research developments regarding the potential binding to PF4 and support those activities wherever possible.

Besides the adenovirus vector, a potential role of the S protein as well as of a predisposition of the patient should be considered. The SARS-CoV-2 S protein has been associated with endothelial inflammation, leukocyte adhesion, release of PF4, hypercoagulation, and thrombosis (Robles 2022; Lei 2021; Perico 2022; Zhang 2020; Grobbelaar 2021; Zheng 2021; Lee 2023), and is hypothesised to be related to adverse effects after COVID-19 vaccination (Trougakos 2022).

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 and is an adverse drug reaction described in the CCDS.

Characterisation of the Risk:

A combination of thrombosis and thrombocytopenia, in some cases accompanied by bleeding, has been observed very rarely following vaccination with Ad26.COV2.S. This includes severe cases of venous thrombosis at unusual sites such as cerebral venous sinus thrombosis (CVST), splanchnic vein thrombosis as well as arterial thrombosis concomitant with thrombocytopenia. Fatal outcomes have been reported. These cases occurred within the first 3 weeks following vaccination, and mostly in individuals <60 years of age.

In the cRMP, for purposes of TTS risk characterisation and presentation of cases, 3 case definitions are used: the interim Brighton Collaboration (BC) case definition (Brighton Collaboration 2021), the CDC working case definition for a Tier 1 or Tier 2 case (Shimabukuro 2021), and the PRAC case definition, which is based on the one proposed by the UK's National Institute for Health and Care Excellence (NICE) (NICE 2022).

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:

Thrombosis with thrombocytopenia syndrome requires specialised clinical management. Healthcare professionals should consult applicable guidance and/or consult specialists (eg, haematologists, specialists in coagulation) to diagnose and treat this condition (CCDS Section Warnings and Precautions).

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.

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. 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. 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:

The mechanism of Ad26.COV2.S-related GBS has not been established. However, as with other vaccines, immune activation is believed to play a role in the development of the disease (Sejvar 2011).

Evidence Source(s) and Strength of Evidence:

Guillain-Barré syndrome has been observed very rarely following vaccination with Ad26.COV2.S both in clinical trials, RWE RCA analysis (see Appendix 6.3), and in the post-marketing setting (Hanson 2022; Miriam 2022). 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 observed versus expected ratios since authorisation to be sufficient evidence for a plausible association between Ad26.COV2.S and GBS.

Guillain-Barré Syndrome 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:

There are no known risk factors for the development of GBS following Ad26.COV2.S vaccination. 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).

Preventability:

The CCDS (Section Warnings and Precautions) states that healthcare professionals should be alert to 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:

Guillain-Barré Syndrome 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.

Venous Thromboembolism

Potential Mechanisms:

A potential mechanism for the occurrence of VTE includes a hypercoagulable state due to an increased 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). 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).

The SARS-CoV-2 S protein has been associated with endothelial inflammation, leukocyte adhesion, release of PF4, hypercoagulation, and thrombosis (Grobbelaar 2021; Lei 2021; Perico 2022; Robles 2022; Zhang 2020; Zheng 2021), and is hypothesised to be related to adverse effects after COVID-19 vaccination (Trougakos 2022).

Recent mechanistic studies (non-clinical studies, and studies using clinical trial samples) conducted by the Company to study the pathogenesis of (vaccine-induced) TTS with potential

relevance to VTE, did not elucidate a clear mechanism of action for VTE following Ad26.COV2.S administration. However, in the context of the Company's mechanistic work on TTS, the hypothesis was tested if TTS and other thrombotic events could have a common mechanism with TTS being the most severe manifestation. Obtained data suggest that a common mechanism is unlikely.

Evidence Source(s) and Strength of Evidence:

Venous thromboembolism 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.

Venous thromboembolism is an ADR described in the CCDS.

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.

Risk Factors and Risk Groups:

In Trials COV3001 and COV3009, underlying risk factors have been identified in participants with VTE such as COVID-19, male gender, old age (>65 years), long-haul travel, thrombophilia, obesity, active malignancy, trauma, previous venous thrombosis, hypertension, and COPD.

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:

Venous thromboembolism 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. 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.

Myocarditis and Pericarditis

Potential Mechanisms:

Infectious diseases account for the majority of cases of myocarditis or pericarditis in previously healthy patients, mainly due to either a direct viral infection or post-viral immune-mediated reaction and myocardial inflammation (Friedrich 2009) and is more frequent in young males. Also viral infection with SARS-CoV-2 can result in acute myocarditis, yet COVID-19 vaccination (including mRNA vaccines and Ad26.COV2.S) was associated with decreased risk of myocarditis, myocardial infarction, and ischaemic stroke after COVID-19 (Jiang 2023; Kim 2022; Patone 2022).

The mechanism of action for vaccine-induced myopericarditis remains to be elucidated. Given the increased incidence among males, differences in hormone signaling might be involved in the pathophysiology (Heymans 2022). It has been proposed that vaccines triggering an intense immune response could be associated with a higher risk of myocarditis (Karlstad 2022). Also, a possible association of circulating S protein with the occurrence of myocarditis has been described (Yonker 2023). Molecular mimicry between the S protein of SARS-CoV-2 and cardiac self-antigens is another possible mechanism. However, only limited experimental evidence supporting this hypothesis exists (Vojdani 2020; Vojdani 2021). The delivery of the Spike gene by different vaccine delivery platforms may result in a different expression pattern of the S protein, thus potentially affecting parameters like levels, kinetics, location and/or post-translational modifications. There are also differences in the biosynthesis, structural features, and presentation of the S protein in current COVID-19 vaccines (Heinz 2021) that may be additionally related to myocarditis/pericarditis incidence.

Evidence Source(s) and Strength of Evidence:

Myocarditis and/or pericarditis have been reported as rare events following vaccination against smallpox, hepatitis B, tetanus, human papillomavirus, and viral influenza and have been documented for COVID-19 vaccines (Mei 2018; Su 2021). A systemic review and meta-analysis revealed higher incidence of myopericarditis following smallpox vaccination but no significant difference after influenza vaccinations compared to COVID-19 vaccination (Ling 2022).

Among COVID-19 vaccines, myocarditis and/or pericarditis has been observed with mRNA vaccines (Husby 2021; Karlstad 2022; Ling 2022; Patone 2022) with an incidence significantly higher in males versus females, in people younger than 30 years, and after a second dose (compared to first or third dose). Additionally, a recombinant adjuvanted protein-based COVID-19 vaccine has been associated with a disproportional myopericarditis induction (Macías Saint-Gerons 2023).

Events of myocarditis and pericarditis have been observed very rarely following vaccination with Ad26.COV2.S both in clinical trials and in the post-marketing setting. Real world evidence data of US claims data sources showed a high level of certainty of an increased risk of myocarditis and pericarditis for males aged 18 to 39 years within 28 days of vaccination with Ad26.COV2.S.

Myocarditis and pericarditis are ADRs described in the CCDS.

Characterisation of the Risk:

An update on the number of cases of myocarditis and pericarditis from clinical trial and post-marketing experience is provided in Section 16.3.1.4, Myocarditis and Pericarditis of this PBRER.

Risk Factors and Risk Groups:

Myocarditis and pericarditis have been reported in association with SARS-CoV-2 infection. Historically, myocarditis and/or pericarditis have been reported as rare events following vaccination against smallpox, hepatitis B and viral influenza (Su 2021). Myocarditis and pericarditis have also been reported with other COVID-19 vaccines (including mRNA-based COVID-19 vaccines and a recombinant adjuvanted protein-based COVID-19 vaccine). Young males appear to be at highest risk, predominantly after receiving the second dose of COVID-19 vaccination. The disease course is self-limiting in a vast majority of cases: 95% of patients show a rapid resolution of symptoms and normalisation of cardiac biomarkers, electro- and echocardiographic findings within days (Klamer 2022).

Preventability:

The CCDS (Section Warnings and Precautions) states that healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis and that vaccinees should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis.

Impact on the Risk-Benefit Balance of the Product:

Myocarditis and/or pericarditis has been reported very rarely in clinical trials and the post-marketing setting following vaccination with Ad26.COV2.S. Based on current clinical trial and post-marketing data and the information in the CCDS, the identified risk of myocarditis and pericarditis does not change the existing established risk-benefit balance for Ad26.COV2.S.

Public Health Impact:

The occurrence of myocarditis and pericarditis is very rare following vaccination with Ad26.COV2.S. Epidemiologic analysis of real world data sources such as electronic medical records and healthcare claims, showed that the risk of myocarditis and pericarditis following COVID-19 vaccination is lower than following natural SARS-CoV-2 infection (Patone 2022). Therefore, the public health impact is currently considered to be low.

Thrombocytopenia, including Immune Thrombocytopenia

Potential Mechanisms:

The mechanistic evidence for vaccine-derived thrombocytopenia is not very well understood. It is suspected to have a strong immune component such as immunostimulation causing alterations in cytokines that abrogate platelet production from megakaryocyte precursors and antigenic mimicry between virus and platelet antigens, giving rise to cross-reactive antiplatelet antibodies (anti-IIb/IIIa) and/or activation of cytotoxic T cells that decrease platelet survival (Wise 2007).

Similar to other autoimmune disorders, molecular mimicry with bacterial or viral proteins might be one reason for the pathogenesis of ITP (Marini 2019).

The SARS-CoV-2 S protein has been associated with endothelial inflammation, leukocyte adhesion, release of PF4, hypercoagulation, and thrombosis (Grobbelaar 2021; Lei 2021; Perico 2022; Robles 2022; Zhang 2020; Zheng 2021), and is hypothesised to be related to adverse effects after COVID-19 vaccination (Trougakos 2022).

Recent mechanistic studies (non-clinical studies, and studies using clinical trial samples) conducted by the MAH to study the pathogenesis of (vaccine-induced) TTS with potential relevance to thrombocytopenia (including ITP), did not elucidate a clear mechanism of action for thrombocytopenia (including ITP) following Ad26.COV2.S administration.

Evidence Source(s) and Strength of Evidence:

Cases of ITP with very low platelet levels (<20,000 per μL) have been reported very rarely after vaccination with Ad26.COV2.S, usually within the first 4 weeks after receiving Ad26.COV2.S. This included cases with bleeding and cases with fatal outcome. Some of these cases occurred in individuals with a history of ITP.

Immune thrombocytopenia is an ADR described in the CCDS.

Characterisation of the Risk:

An update on the number of cases of ITP from clinical trial and post-marketing experience is provided in Section 16.3.1.5, Thrombocytopenia, including Immune Thrombocytopenia of this PBRER.

Immune thrombocytopenia is a challenging diagnosis, with no unique identifying features when it occurs after vaccination. Unlike vaccine-induced thrombosis and thrombocytopenia, ITP is a diagnosis of exclusion. There is no specific test that confirms the diagnosis, and clinicians therefore rely on the lack of distinguishing features of other diseases (Pishko 2021).

Risk Factors and Risk Groups:

Limited data from post-marketing experience with Ad26.COV2.S, including literature, 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) provides guidance to healthcare professionals to be alert to signs and symptoms of thrombocytopenia.

In addition, 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:

Immune thrombocytopenia 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 and adequate risk minimisation via the CCDS is considered sufficient to manage this risk. 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.

16.4.2. Characterisation of Important Potential Risks

Important potential risks that may be associated with the use of Ad26.COV2.S include the following:

Vaccine-associated Enhanced Disease (VAED), Including Vaccine-associated Enhanced Respiratory Disease (VAERD)

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-vaccines (Chin 1969; Fulginiti 1969; Kapikian 1969; Kim 1969; Su 2020; Agrawal 2016; Bolles 2011; Deming 2006; Honda-okubo 2015; Houser 2017). 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.

VAED/VAERD has not been described in association with Ad26.COV2.S and has not been confirmed from any other late phase clinical trial of other COVID-19 vaccines.

Studies in Ad26.COV2.S-immunised Syrian hamsters and 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 2021).

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 non-clinical 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 participants 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.

16.4.3. Description of Missing Information

Use During Pregnancy

Evidence source:

There is limited experience with the use of Ad26.COV2.S in pregnant women.

Animal data from the EF-PPND toxicity study with Ad26.COV2.S indicate no adverse effect of Ad26.COV2.S on reproductive performance, fertility, ovarian and uterine examinations, or parturition. In addition, there was no adverse effect of vaccination on foetal body weights, external, visceral and skeletal evaluations, or on postnatal development of the offspring.

Pregnancy at baseline was not an exclusion criterion in Trial COV2008, and Trial COV2004 is a trial in pregnant women. Up to the cut-off date of 24 February 2022, 23 women who were pregnant at baseline received at least 1 dose of Ad26.COV2.S (cross-dose level pooling; all dose levels). Of

the pregnancies reported in Trial COV2004 (n=22), 9 were still ongoing, 11 had a normal outcome, and 2 had an outcome of preterm neonate (1 without complications and 1 with complications). The pregnancy reported in Trial COV2008 had an outcome of premature without complications. No safety concerns have been identified in this population.

Any case of study vaccine exposure during pregnancy was included in the Company's global safety database when reported during the course of the trials. As of the cut-off date of 24 February 2023, 131 unique pregnancies were retrieved from Company-sponsored clinical trials post-baseline; 111 involved maternal exposure and 20 were partner pregnancies; all following Ad26.COV2.S administration. Overall, reported outcomes were live birth (n=53), spontaneous abortion (n=14, including 1 case of missed abortion due to Trisomy 21), elective abortion (n=4, 2 due to congenital anomalies: skeletal dysplasia and unspecified anomaly), intrauterine death, live birth with congenital anomaly (congenital tracheomalacia and ventricular septal defect) (n=2 each), ectopic pregnancy (n=1), and unknown (n=56). Of note, 1 participant reported a twin pregnancy during the trial (1 with an outcome of spontaneous abortion, 1 with an unknown outcome).

Up to the cut-off date of 24 February 2023, 731 unique cases reporting use in pregnancy were retrieved from post-marketing sources (including spontaneous and solicited primary and booster cases); 729 involved maternal exposure and 2 were partner pregnancies. Of these unique pregnancy cases, 233 cases reported 237 outcomes due to 4 twin pregnancies. One twin pregnancy resulted in a spontaneous abortion of one twin and a live birth without congenital anomaly of the other and are included in the following counts. The outcomes included live birth without congenital anomaly (n=146 [including 1 set of twins]), spontaneous abortion (n=64 [including 2 sets of twins]), live birth with congenital anomaly (n=16), ectopic pregnancy (n=5), blighted ovum (n=2), and 1 case each of still birth without congenital anomaly, still birth with congenital anomaly, maternal death, and intrauterine death. Of the 64 spontaneous abortion outcomes, there were 14 outcomes with exposure before conception, 26 outcomes with exposure during the first trimester of pregnancy, and for the remaining 24 outcomes timing of vaccine exposure was not reported.

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.

Anticipated risk/consequence of the missing information:

Based on the nonreplicating nature of the vaccine and on non-clinical and limited clinical and post-marketing data available to date, 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 fetuses 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) are ongoing to 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 is provided in Section 16.3.5.1, Use During Pregnancy of this PBRER.

Use in Breastfeeding Women

Evidence Source:

Breastfeeding women were excluded from all clinical trials, except from the Phase 2 trial COV2008 and the Phase 3 trials COV3001, COV3003, and COV3009. Up to the cut-off date of 24 February 2022, 718 women who were breastfeeding at baseline have received at least one dose of Ad26.COV2.S (cross-dose level pooling; all dose levels). No safety concerns have been identified for breastfeeding women. However, safety data for their breastfed children is currently not available.

Up to the cut-off date of 24 February 2023, there have been 137 unique cases (post-marketing spontaneous or noninterventional cases) of exposure to Ad26.COV2.S via breastfeeding. No safety signals were identified.

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.

A small subset of participants within Trial COV2004 will be followed up during breastfeeding to assess the transfer of antibodies via breast milk. Breastfeeding women were also allowed to participate in Trials COV2008, COV3001, COV3003, and COV3009 to characterise the safety profile of Ad26.COV2.S in this subpopulation. An update on the number of cases from clinical trial and post-marketing experience in use in breastfeeding women is provided in Section 16.3.5.2, Use in Breast Feeding Women of this PBRER.

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 included in Trials COV2008, COV3001, and COV3009.

The efficacy of Ad26.COV2.S may be lower in immunosuppressed individuals.

The final analysis results of the double-blind phase in trial COV3001 showed that, overall, the vaccine was efficacious against molecularly confirmed moderate to severe/critical COVID-19 with onset at least 14 days and 28 days after vaccination across demographic and baseline characteristics subgroups. An exception was noted for HIV-positive participants (with a stable/well-controlled HIV infection) in which the VE was lower. Due to few COVID-19 cases in HIV-positive participants, this conclusion should be interpreted with caution. No clinically relevant difference in the reactogenicity profile could be observed in HIV-infected versus HIV-negative participants (COV3001 CSR 2021).

In the FAS of Trial COV3001, SAEs were reported in 8 (1.3%) out of 604 HIV-infected participants 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 (COV3001 CSR 2021).

Based on the final analysis results of the double-blind phase in trial COV3009, no conclusion can currently be made about VE in HIV-infected participants due to the limited number of HIV-positive participants. In the FAS of trial COV3009, SAEs were reported in 3 (1.4%) out of 213 HIV-infected participants 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 (COV3009 CSR Dec 2021).

Of the 65,490 participants in the cross-dose level pooling who received at least one dose of Ad26.COV2.S (all dose levels), 1,440 (2.2%) participants had a stable/well-controlled HIV infection. Participants with other immunodeficiencies were included at low numbers.

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. There were no specific safety concerns and no notable differences between HIV-infected and healthy participants with regard to reporting frequency or severity of AEs at any timepoint from the 2 pivotal trials.

Use in immunocompromised patients will be further characterised in the post-authorisation safety studies COV4003 and COV4001 and effectiveness study COV4004.

An update on the number of cases from clinical trial and post-marketing experience in use in immunocompromised patients is provided in Section 16.3.5.3, Use in Immunocompromised Patients.

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.

Participants with clinical conditions stable under non-immunomodulator treatment (eg, autoimmune thyroiditis, autoimmune inflammatory rheumatic disease such as rheumatoid arthritis) were eligible for enrollment in Phase 3 trials COV3001 and COV3009 at the discretion of the investigator. Of the 21,898 participants in the FAS of trial COV3001 who received Ad26.COV2.S ($5x10^{10}$ vp dose level), 552 participants had a medical history of at least 1 immune-mediated/autoimmune disorder at baseline. Of these 552 participants, 5 (0.9%) reported an exacerbation (flare-up) of their pre-existing autoimmune disorder during the double-blind phase of the trial. Of the 15,708 participants in the FAS of trial COV3009 who received at least 1 dose of Ad26.COV2.S ($5x10^{10}$ vp dose level), 458 participants had a medical history of at least 1 immune-mediated/autoimmune disorder at baseline. Of these 458 participants, 2 (0.4%) reported an exacerbation (flare-up) of their pre-existing autoimmune disorder, during the double-blind phase of the trial.

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.

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 65,490 participants in the cross-dose level pooling who received at least one dose of Ad26.COV2.S (all dose levels), 25,737 (39.3%) participants had 1 or more comorbidities associated with an increased risk for severe COVID-19. Of these 25,737 participants,

11,102 (43.1%) were aged ≥60 years, 6,378 (24.8%) were ≥65 years, and 1,216 (4.7%) were aged ≥75 years.

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 participants enrolled. Of the 19,577 participants in the Per Protocol set who received Ad26.COV2.S (5x1010 vp dose level), 6 (<0.1%) were defined as frail and 2,147 (11.0%) were defined as pre-frail. Of the 6 frail participants, 5 (83.3%) were aged ≥60 years. Of the 2,147 pre-frail participants, 1,338 (62.3%) were aged ≥60 years (COV3001 CSR 2021).

Population in need of further characterisation:

Safety data will be further collected in individuals who are frail due to age or debilitating disease in the post-authorisation safety studies COV4003 and COV4001, and through routine pharmacovigilance.

An update on the number of cases from clinical trial and post-marketing experience in use in frail patients is provided in Section 16.3.5.5, Use in Frail Patients With Comorbidities (eg, Chronic Obstructive Pulmonary Disease, Diabetes, Chronic Neurological Disease, Cardiovascular Disorders).

Long-term Safety

Evidence source:

There are limited data available on the long-term safety of Ad26.COV2.S. Participants in Trial COV3001 were followed for at least 2 years. No new safety concerns were identified. Note that due to several study limitations, no conclusions on group comparisons could be drawn.

Based on long-term safety data from other Ad26-based vaccines (at least 6 months up to 5 years post-vaccination in clinical trials), no long-term safety issues have been identified (Adenoviral Vaccine Safety Database V7.0 2022).

Population in need of further characterisation:

The long-term safety of Ad26.COV2.S is not 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 Trial COV3009 following administration of Ad26.COV2.S, and for up to 1 year in the post-authorisation safety studies COV4003 and COV4001.

Participants of Trial COV3009 who initially received placebo were unblinded and offered a single dose of Ad26.COV2.S (crossover vaccination), since the vaccine has received an EUA in the United States and conditional Marketing Authorisation in the European Union/EEA. All

participants have been encouraged to remain in the trial and will be followed for safety as originally planned up to 2 years from time of enrollment into study.

An update on the number of cases from clinical trial and post-marketing experience in use in long-term safety is provided in Section 16.3.5.7, Long-Term Safety.

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.

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) was completed during the reporting interval of the PBRER. No additional safety concerns were identified following the coadministration of the 2 vaccines.

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 15.3, Use with Concomitant Vaccination of this PBRER.

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 interval for Ad26.COV2.S.

17. BENEFIT EVALUATION

As of 14 January 2024, there have been 774,291,287 confirmed cases of COVID-19 globally, including 7,019,704 deaths. As of 26 November 2023, over 13.59 billion vaccine doses have been administered. (WHO 2024a). In Europe, as of 14 January 2024, there have been a total of 278,731,686 confirmed cases of COVID-19, and 2,267,429 cases of COVID-19 related deaths (WHO 2024b).

In the US, as of 14 January 2024, there have been a total of 103,436,829 confirmed cases of COVID-19 reported, and 1,165,780 cases of COVID-19 related deaths reported. A total of 676,728,782 vaccine doses have been administered. (CDC 2024)

Over the course of the SARS-CoV-2 pandemic, changes in SARS-CoV-2 Spike protein 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.

From mid-2020, the emergence of variants in several countries, such as UK, RSA, Brazil, India, US, Peru, and 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. Previous VOCs include Alpha (B.1.1.7, earliest detection: UK), Beta (B.1.351, earliest detection: Republic of South Africa [RSA]), Delta (B.1.617.2, earliest detection: India), Gamma (P.1, earliest detection: Brazil) and Omicron parent lineage (B.1.1.529, earliest detection: South Africa). 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). On 15 March 2023, WHO updated their COVID-19 variant tracking system with changes to the definitions of VOC and VOI, to add a new category (variant under monitoring; VUMs) to track Omicron sublineages (WHO 2023c). In addition to the Omicron sublineage XBB.1.16 being classified as a VOI on 17 April 2023, and the pango lineages EG.5, BA.2.86, and JN.1 being classified as VOIs on 09 August 2023, 21 November 2023, and 09 February 2024, respectively, a number of other Omicron sublineages are designated as VUMs as of 17 May 2023 (WHO 2023d).

The emergence of SARS-CoV-2 variants with multiple mutations in the S protein have raised concerns because of their potential to increase transmission rates and/or cause 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

The efficacy, immunogenicity, and safety data from the pivotal, randomised, double-blind, placebo-controlled, Phase 3 COV3001 study in adults ≥18 years of age 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. Key efficacy data from the primary analysis (cut-off date 22 January 2021) 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 the 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 circulating during the conduct of the study.

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 COV3001 study, 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

Company-Sponsored Clinical Efficacy Studies

At the time of the final efficacy analysis of the double-blind phase of Study COV3001 (cut-off date 09 July 2021) 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 (cut-off date 25 June 2021) 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.

Study 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) 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 (68%, 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 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 (Verani 2022; Acuti Martellucci 2022; Adams 2022; Gray 2022; Kissling 2021; Lewis 2022; Vokó 2022; Wright 2022; Yi 2022; Zheutlin 2022).

Overall, estimates from real world studies during periods of time when surveillance studies have indicated that Omicron/Omicron sub-variants were in circulation show that VE of both a single and booster dose of Ad26.COV2.S was moderate with indications of waning over time against COVID-19 infection and higher against hospitalisations and intensive care unit admissions, with a booster dose showing a marked increase in VE compared to a single dose (DeSantis 2023; Ito 2023; Kompaniyets 2022; Lin 2022).

Study VAC31518COV3009

Efficacy results from final analysis of the double-blind phase (ie, primary analysis with cut-off date of 25 June 2021) of ongoing Phase 3 Study 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 final analysis of the double-blind phase, 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 Ad26.COV2.S, 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 Ad26.COV2.S group and placebo group, respectively) was not demonstrated. There were no reference strain cases in either the Ad26.COV2.S 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 from these clinical studies 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 circulating during the conduct of these clinical studies.

Note that while the analyses of Delta cases from these clinical studies 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 (DeSantis 2023; Ito 2023; Kompaniyets 2023; Lin 2022; Lewis 2022).

Real World Evidence (Effectiveness) Studies

In addition to the clinical efficacy studies (COV3001, COV3009 and COV4004), the Company has conducted a review 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.

Study 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 160 million patient lives submitted by US providers of inpatient, outpatient, pharmacy, and laboratory services from 01 March 2021 to 30 April 2022 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 and the initial emergence of the Omicron BA.1 and BA.2 subgroups.

Study VAC31518COV4004

Final results were available for this study, multi-center, multi-country, hospital-based case-control study with test negative case-control design to assess the absolute effectiveness of a single-dose of Ad26.COV2.S in comparison to no vaccine against laboratory-confirmed SARS-CoV-2 SARI hospitalisations as well as estimate effectiveness for different age groups, those identified with certain chronic conditions, immunocompromised individuals, duration since vaccination, and related to specific SARS-CoV-2 variants.

The final results from this study with data collection through February 2023 demonstrated that a single-dose of Ad26.COV2.S provided protection against laboratory confirmed SARS-CoV-2 SARI hospitalisations. This protection persisted for up to 6 months after vaccination. No significant differences were seen when stratified by age, chronic medical condition, time since dose, or period of specific SARS-COV-2 variants. There was lack of precision, particularly for stratified analyses, due to the small number of enrolled vaccine recipients.

Study VAC31518COV4019

The 6-month interim results from a Company-sponsored COV4019 study captured a study period spanning 20 October 2020 to 02 May 2022. During this study period, surveillance data indicated that Omicron strains BA.1, BA.2, BA.2.12.1, and BA.5 were in circulation. Overall, results indicated that both homologous and heterologous booster doses of Ad26.COV2.S were found to be an effective strategy in preventing COVID-19-related hospitalisation and medically attended COVID-19 for at least 6 months. In addition a booster dose of Ad26.COV2.S provides additional protection against COVID-19-related hospitalisation and medically attended COVID-19 in the real world setting compared to a single Ad26.COV2.S dose.

Studies VAC31518COV3012 (Sisonke [Together]) and VAC31518COV3021 (Sisonke 2)

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 17 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 the Beta and the Delta and Omicron breakthrough infection patterns in SISONKE HCWs, with Delta (60%) and Omicron (B.1.1.529, 67%) producing a higher proportion of breakthrough infections (BTI)-related hospitalisations in individuals between 31 to 54 years of age than Beta (51%) (Goga 2021; Goga 2022). A concomitant reduction was observed in the 55+ age group (46% during Beta, to 33% during Delta, and 19% during Omicron [p<0.001]). During Omicron, 91% hospitalised HCWs required general ward care, 6% high care and 3% intensive care. This was significantly different from 89% general ward care, 4% high care, and 7% intensive care during Delta and 78% general care, 7% high care and 16% intensive care during Beta (p<0.001). During Beta and Delta, 43% of hospitalised HCW needed supplementary oxygen and 7 to 8% needed ventilation, compared with 16% and 0.2% respectively during the Omicron period (p<0.001).

The SISONKE 2 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 South Africa (Gray 2022). Vaccine effectiveness of the Ad26.COV2.S vaccine booster was estimated using a test negative design. Vaccine effectiveness (95%CI) against COVID-19 hospital admission was 55% (22% to 74%) when evaluated 0 to 13 days after the booster and increased to 74% (57% to 84%) and 72% (59% to 81%) when evaluated 14 to 27 days and 1 to 2 months after the booster, respectively. Vaccine effectiveness (95% CI) against intensive care unit admission or high care was 69% (26% to 87%) at 14 to 27 days and 82% (57% to 93%) at 1 to 2 months after the second dose.

Summary of Evidence from Additional Real world Studies

Results of additional RWE studies that report Ad26.COV2.S 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 single homologous and heterologous doses 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 (DeSantis 2023; Ito 2023; Kompaniyets 2023; Lin 2022; Lewis 2022). Single dose Ad26.COV2.S VE against infection were reported to be lower during Omicron-emerging and Omicron-predominated periods. Vaccination remained more effective in preventing hospitalisation and death during the Omicron-emerging and Omicron-predominated periods. Vaccine effectiveness against COVID-19 infections and COVID-19-related hospitalisations were observed in fully vaccinated individuals who received a booster dose. Fully vaccinated individuals who received heterologous Ad26.COV2.S or mRNA booster vaccines showed an increase in VE compared with homologous dose Ad26.COV2.S or mRNA vaccines during the Omicron periods. 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 against VOCs seen with the single dose Ad26.COV2.S vaccine in COV4002.

Key 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.

Study VAC31518COV2008

Study COV2008 is a randomised, double-blind, multicentre, Phase 2 study in adults ≥18 years of age in the US, in which a homologous Ad26.COV2.S booster was administered ≥6 months after primary vaccination in Cohort 1 or Ad26.COV2.S booster was administered ≥6 months after primary vaccination with 2 doses of BNT162b2 in Cohort 2.

Data from the primary analysis of COV2008 Cohort 1 have demonstrated NI of neutralising antibody titres 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 titres and response rates against the Beta variant at Day 15 post-homologous booster are consistent with non-inferiority criteria compared to neutralising antibody titres and response rates at Day 29 after primary vaccination. Titres 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 titres 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 titres following a homologous 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.

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. Titres 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 BA.1 variant were lower than those against the reference strain, Delta variant, and Beta variant after homologous (Cohort 1) or heterologous (Cohort 2) booster vaccination with Ad26.COV2.S at the 5×10^{10}vp dose level. However, the kinetics of the neutralising antibodies against the Omicron BA.1 variant were similar to neutralising antibodies against the other strains. By Day 29 post-homologous booster, neutralising antibody titres were maintained at Day 15 levels, while titres and responder rates post heterologous booster increased between Day 15 and Day 29. Non-powered descriptive analyses indicate that by Day 15, neutralising antibody titres and response rates against the Omicron BA.1 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 was further supported by data from DMID 21-0012, COV-BOOST, RRH-001 and by data from the literature.

Non-Company-Sponsored Interventional Studies

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 and from Study RRH-001 in which a heterologous boost was administered after primary vaccination with an inactivated whole-virion COVID-19 vaccine. 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 (Beta, Delta, and Omicron BA.1).

Literature Review

Finally, homologous and heterologous boosting with Ad26.COV2.S are further supported by data from the literature (Mod5.3.5.4/Literature Summary Report/Systematic Literature Review of Immunogenicity Data Post-Homologous or Post Heterologous Boost With Janssen COVID-19 Vaccine or Other [mRNA] COVID-19 Vaccines; Tan 2022). 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 BA.1 and BA.2, compared with pre-boost timepoint. Neutralising antibodies were boosted by all vaccine combinations, including against Omicron strains, with a modest boosting being seen with Ad26 homologous boosting. 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.

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.

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 disease 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 RSA (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 potential to increase transmission rates and/or cause 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 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 07 January 2024, there have been 774,075,242 confirmed cases of COVID-19, including 7,012,986 deaths worldwide (WHO 2023a). In Europe, as of 21 November 2023, there have been a total of 278,300,338 confirmed cases of COVID-19, and 2,260,650 cases of COVID-19 related deaths (WHO 2023b).

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 (WHO 2023e; Genomic epidemiology of SARS-CoV-2 2023). However, the case fatality rate is affected by factors that include age, underlying pre-existing 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.

Main Existing Treatment and Prevention Options:

Despite the ever-growing number of available treatment options, an emphasis remains on disease prevention for global control of SARS-CoV-2. Since transmission of SARS-CoV-2 occurs primarily through respiratory secretions (droplets) and to a lesser extent via contact with contaminated surfaces, covering coughs and sneezes as well as social distancing (maintaining a distance of 1.5 m or 6 feet from others) can reduce the risk of transmission. Mouth and nose coverings, if properly pursued, may further reduce the spread of droplets from infectious individuals to others when social distancing is not possible. Furthermore, frequent handwashing and the use of hand sanitiser (>60% alcohol) are effective in reducing acquisition (CDC 2020). Finally, frequent testing for SARS-CoV-2, contact tracing, and local quarantine measures have shown to be effective in reducing virus spread.

Prophylaxis

As of 01 December 2023, besides the Janssen COVID-19 vaccine, the following vaccines have received (conditional) marketing authorisation from EMA (EMA 2023) and/or from the UK MHRA (NHS 2023a): the mRNA-based BNT162b2 vaccine Comirnaty from Pfizer and BioNTech and adapted vaccines, the mRNA-1273 vaccine Spikevax from Moderna Inc and adapted vaccines, the ChAdOx1-S (recombinant) vaccine Vaxzevria from AstraZeneca, the (recombinant) vaccine Nuvaxovid from Novavax and adapted vaccine, the (recombinant) vaccine VidPrevtyn Beta from Sanofi Pasteur, and the (recombinant) vaccine Bimervax from Hipra Human Health.

As of 03 October 2023, the following vaccines have received EUA or full regulatory approval from the FDA: Spikevax and adapted vaccine (Moderna Inc.), Comirnaty and adapted vaccine (Pfizer and BioNTech), and Novavax COVID-19 vaccine and adapted vaccine (Novavax) (FDA 2023a).

As of 16 June 2023, besides the Janssen COVID-19 vaccine, the following vaccines have received WHO emergency use listing: Comirnaty and adapted vaccines (BioNTech), Vaxzevria

(AstraZeneca), the ChAdOx1-S (recombinant) vaccine Covishield (Serum Institute of India), Spikevax (Moderna Inc), the inactivated COVID-19 (Vero Cell) vaccine (Beijing Institute of Biological Products), the inactivated COVID-19 (Vero Cell) vaccine CoronaVac (Sinovac Life Sciences), the whole-virion inactivated coronavirus vaccine Covaxin (Bharat Biotech International), the SARS-CoV-2 rS protein nanoparticle (recombinant) vaccine Covovax (Serum Institute of India), Nuvaxovid and adapted vaccine (Novavax), the Ad5-nCoV-S (recombinant) vaccine Convidecia (CanSino Biologics), and the recombinant protein subunit vaccine SKYCovione (SK Bioscience) (WHO 2023a). On 09 October 2023, the Bimervax vaccine (Hipra Human Health) obtained the prequalification status from WHO (WHO 2023b).

Therapeutics

As of 08 August 2022, the following treatments received (conditional) approval by the EMA for the treatment of COVID-19: remdesivir (Veklury), tixagevimab/cilgavimab (Evusheld), anakinra (Kineret), PF-07321332/ritonavir (Paxlovid), regdanvimab (Regkirona), tocilizumab (RoActemra), casirivimab/imdevimab (Ronapreve), and sotrovimab (Xevudy) (EMA 2023). In addition, EMA endorses the use of dexamethasone in COVID-19 patients on oxygen or mechanical ventilation (EMA 2020b). The following COVID-19 treatments are approved for use in the United Kingdom for people with COVID-19 who are at the highest risk of becoming seriously ill: remdesivir (Veklury), nirmatrelvir/ritonavir (Paxlovid), sotrovimab (Xevudy), and molnupiravir (Lagevrio) (NHS 2023b).

As of 25 May 2023, remdesivir (Veklury), baricitinib (Olumiant), and tocilizumab (Actemra), and nirmatrelvir/ritonavir (Paxlovid) are the only drugs currently approved by FDA for the treatment of COVID-19 (FDA 2023b; FDA2023c).

In addition, the following medical products have been granted EUA to treat COVID-19: the antiviral molnupiravir, the IL-1 receptor antagonist anakinra, the monoclonal anti-human complement factor C5a antibody vilobelimab, COVID-19 convalescent plasma. The following medical products had been granted EUA but are currently not authorised in any US region due to the high frequency of circulating SARS-CoV-2 variants that are non-susceptible to the product: casirivimab plus imdevimab, tixagevimab plus cilgavimab, sotrovimab, and bebtelovimab (FDA 2023a; FDA 2023b; FDA 2023c).

Apart from the above drugs and biological products for the treatment of COVID-19, other medicinal products, including but not limited to sedative drugs, personal protective equipment, ventilators, and diagnostic tests, received EUA because of the urgent medical need caused by the COVID-19 pandemic (FDA 2023a).

The National Institute of Health issued COVID-19 treatment guidelines including recommendation strategies for the use of different therapeutics, for the management of patients with different severities of disease (COVID-19 Treatment Guidelines Panel 2023).

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 7 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. The final results from Janssen's multi-country TNCC study (VAC31518COV4004) with data collection through February 2023 demonstrated that a single-dose of Ad26.COV2.S provided protection against laboratory confirmed SARS-CoV-2 severe acute respiratory infection (SARI) hospitalisations. This protection persisted for up to 6 months after vaccination. Final results (up to 12 months after vaccination; median follow-up ranging from 243 days to 268 days) 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 demonstrated effective and stable VE for the single-dose Ad26.COV2.S, based on month-on-month analysis and Kaplan-Meier plots through the end of September 2022.

Additionally, final results (with 12 months of follow-up time from the date of booster vaccination for an exposed individual and the corresponding date for the matched individual in the referent group) for the Study VAC31518COV4019, demonstrated that both homologous and heterologous booster vaccines provided protection against COVID-19 related hospitalisations for up to 12 months.

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 titres 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. Neutralising antibody responses against the reference strain elicited by either homologous or heterologous booster vaccination were durable for 6 months to one year in the final analysis. Beta and Omicron BA.1 variant neutralising antibody titres were also increased after a homologous boost compared to pre-boost titres albeit lower than for the reference strain and Delta variant.

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 BA 1 variant were lower than those against the reference strain, Delta variant, and Beta variant after homologous (Cohort 1) or heterologous (Cohort 2) booster vaccination with Ad26.COV2.S at the 5×10^{10}vp dose level. However, the kinetics of the neutralising antibodies against the Omicron BA.1 variant were similar to neutralising antibodies against the other strains. Immunogenicity data showed that neutralising antibody responses against Omicron sub-variants BA.2 and BA.5 can be boosted by a single booster dose of Ad26.COV2.S (as assessed by validated psVNAs.) Neutralising antibodies against these sub-variants up to 15 days post-boost showed comparable results vs. wild type virus.

In COV3005, immunological non-inferiority of concomitant administration of the Ad26.COV2.S vaccine and a standard-dose influenza vaccine versus administration of the standard-dose influenza vaccine alone was demonstrated for 3 of the 4 influenza vaccine strains studied (A/Cambodia [H3N2], B/Victoria [B/Victoria], and B/Phuket [B/Yamagata]). The study marginally failed to demonstrate non-inferiority for the HI titers of the A/Victoria (H1N1) strain (upper bound was slightly higher than 1.5 [ie, 1.53]). Although non-inferiority was not met for the H1N1 strain,

seroconversion and seroprotection rates against the 4 influenza vaccine strains were comparable 28 days after concomitant administration of the Ad26.COV2.S and influenza vaccines and 28 days after administration of the influenza vaccine alone in the standard-dose groups. Thus, the lower H1N1 HI titers with concomitant administration were considered as clinically not relevant. Non-inferiority of the binding antibody response against SARS-CoV-2 after concomitant administration of Ad26.COV2.S vaccine and a seasonal quadrivalent standard-dose influenza vaccine versus the administration of Ad26.COV2.S vaccine administered alone was also demonstrated in COV3005.

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 at least 2 months after primary vaccination, supporting the hypothesis that antibody levels correlate with protection. For the reference strain and Delta, Beta, and Omicron BA.1 variant, heterologous booster vaccination with Ad26.COV2.S elicited higher neutralising antibody titres 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 $\geq$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 at least 2 months after primary vaccination.

Furthermore, 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.

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 (LMIC) there is still a high need for both primary and booster vaccination and Therefore, Ad26.COV2.S remains a valuable and relevant asset to address the COVID-19 pandemic.

Key Risks

The safety concerns from the current cRMP (version 8.0; dated 06 February 2024) are provided in Table 81:

Table 81: Safety Concerns at the End of the Reporting interval

Important Identified Risks	Thrombosis with thrombocytopenia syndrome Guillain-Barré syndrome Venous thromboembolism Myocarditis and pericarditis Thrombocytopenia, including immune thrombocytopenia [a]
Important Potential Risks	Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD)
Missing Information	Use during pregnancy Use in breastfeeding women Use in immunocompromised patients Use in patients with autoimmune or inflammatory disorders Use in frail patients with comorbidities (eg, chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders) Long-term safety

a: Immune thrombocytopenia has been reclassified from an important potential risk to an important identified risk and has been renamed as "Thrombocytopenia, including immune thrombocytopenia".

The safety concerns from the EU-RMP (version 7.1, dated 13 June 2023) in place at the end of the renewal reporting interval are presented in Section 16.1.2, Summary of Safety Concerns at the End of the Reporting interval.

During the reporting interval, the Company has conducted a cumulative evaluation on bleeding disorders and thrombocytopenic events. Based on the available safety data, the Company has concluded there is a reasonable possibility of a causal association between Ad26.COV2.S and thrombocytopenia, in some instances accompanied by bleeding. Therefore, the important potential risk of "Immune thrombocyopenia" has been reclassified as an important identified risk and renamed "Thrombocytopenia, including immune thrombocytopenia".

Overall Assessment of Risk

The initial safety profile of Ad26.COV2.S vaccine was established at the time of the first authorisation based on safety data at the time of the primary analysis of Study COV3001, complemented by safety data from the then ongoing Phase 1, 2 and 3 studies. Since then, additional information became available through routine safety pharmacovigilance activities (such as signal detection) for which the results were reflected in updates of the cRMP, EU-RMP, Summary Safety Reports, PBRERs, and amendments to the Product Information.

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 in COV3001) 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 in COV3001) 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.

The safety of a homologous Ad26.COV2.S booster dose has been evaluated in several clinical studies including Study COV3009 and Study COV2008. Overall, the solicited adverse reaction profile for the homologous booster dose was similar to that after the first dose and there were no new safety signals identified. The safety of a heterologous Ad26.COV2.S booster dose after primary vaccination with 2 doses of an mRNA COVID-19 vaccine has been evaluated in Study COV2008 and 2 independent studies (COV-BOOST and DMID 21-0012 studies). There were no new safety concerns identified; however, a trend towards an increase in frequency and severity of solicited local and systemic AEs after the heterologous booster dose was observed when compared with the homologous booster dose of Ad26.COV2.S. The safety of a heterologous Ad26.COV2.S booster dose after primary vaccination with an adenoviral vector-based COVID-19 vaccine was also evaluated in the COV-BOOST study; no new safety concerns were identified.

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, VTE, and myocarditis and pericarditis occurred very infrequently, are adequately monitored, and do not outweigh the significant benefits of vaccination with Ad26.COV2.S. The current post-authorisation exposure is insufficient to establish differences in the onset and severity of these very rare ARs 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 21 January 2024, over 13,463,821,163 doses of the COVID-19 vaccine have been administered (CDC 2023; ECDC 2023; KDCA 2023). Increasing experience based on spontaneous/solicited post-marketing reporting of AEs, have led to the identification of

SAEs/reactions such as TTS, GBS, ITP, and myocarditis/pericarditis. 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.

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 caused by SARS-COV-2 virus in adults ≥18 years of age. This assessment is based on the following considerations:

- A single dose of Ad26.COV2.S has demonstrated long cellular immunity and protective efficacy against emerging variants (assessed most recently at the beginning of the Omicron period).
- The very rare occurrence of the known safety concerns for the vaccine (mainly identified following primary immunisation). Many of these safety concerns (thrombotic and coagulation disorders, GBS and myocarditis/pericarditis) have also been observed following natural SARS-COV2 infection, with a much higher incidence and severity than following vaccination.
- The current usage pattern of Ad26.COV2.S is centred mainly in LMICs. The vaccine's profile (single-dose, multi-vial, adaptable to existing cold chain infrastructure) allows for mass primary vaccination against SARS-COV2 even in remote communities currently under vaccinated against SARS-COV2.S.

19. CONCLUSIONS AND ACTIONS

During the reporting interval of this PBRER, a type II variation to update EU PI and EU-RMP of Ad26.COV2.S to reflect the IIRs of myocarditis and pericarditis was submitted. During the reporting interval, CCDS was updated thrice to include "myocarditis and pericarditis", "immune thrombocytopenia", and "reactogenicity" in the adverse reaction section of CCDS. Also, "transvere myelitis" was added to the post-marketing section, warning related to an increased risk of myocarditis/pericarditis in males younger than 40 years of age was added, and text for concomitant use with other vaccines was updated in the "interaction" section. The Company will continue to monitor the safety profile of Ad26.COV2.S to further characterise important identified and potential risks and identify emerging risks if warranted.

Ad26.COV2.S continues to have a favourable benefit-risk profile when used as recommended in the currently approved indication(s). The Company will continue to monitor suspected adverse reactions in association with the use of Ad26.COV2.S. Continuous Company safety monitoring will ensure that updated safety information is available.

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