JCOVDEN : Periodic safety update report assessment

25 August 2022 to 24 February 2023

This document consists of:

1. The PRAC assessment report of the JCovden periodic safety update report (PSUR) covering the period 25 August 2022 to 24 February 2023, 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/420472/2023
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC PSUR assessment report

Procedure no.: EMEA/H/C/PSUSA/00010916/202302

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

Period covered by the PSUR: 25/08/2022 To: 24/02/2023

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:	1 June 2023	1 June 2023
☐	PRAC Rapporteur's preliminary assessment report (AR)	31 July 2023	19 July 2023
☐	MS/PRAC members and MAH comments	30 August 2023	30 August 2023
☒	PRAC Rapporteur's updated assessment report following comments	14 September 2023	N/A
☐	Oral explanation	n.a	n.a
☐	PRAC recommendation	28 September 2023	28 September 2023

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 fourth Periodic Safety Update Report (PSUR) for COVID-19 vaccine Janssen (Ad26.COV2.S); covering data for the period from 25 August 2022 to 24 February 2023.

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 120,564,550 doses of Ad26.COV2.S vaccine were estimated to have been distributed worldwide. A total of 611,193,650 doses of Ad26.COV2.S vaccine were distributed worldwide from launch to 28 February 2023. A total of 53,047,996 doses of Ad26.COV2.S vaccine were administered worldwide from launch to 28 February 2023.

Changes of the product information have been made during this PSUR period in the frame of procedure II/0064 to introduce an heterologous booster with Ad26.COV2.S following primary vaccination with another adenoviral vector-based vaccine and to provide updated follow-up data from studies which were included in variation EMEA/H/C/005737/II/0033. As a consequence, sections 4.2, 4.8 and 5.1 of the SmpC have been updated. The PL has been updated accordingly. Furthermore, ADR frequencies, listed in section 4.8 were updated in the frame of procedure II/0060.

During this reporting interval 6 signals were started, i.e.,

- cutaneous vasculitis (started by the MAH in Sep 2022, closed Feb 2023) – the signal led to an update of the MAHs CCDS. The evaluation of this signal is ongoing and will be presented in the next PBRER. Recently, small vessel vasculitis has been added to the SmPC, section 4.8.
- cerebral hemorrhage (MAH internal investigation, started Dec 2022, ongoing),
- transverse myelitis (Dec 2022, closed January 2023) – the MAH has added this term to the own CCDS. Transverse myelitis has already been listed in the SmPC, section 4.8.
- Heavy menstrual bleeding (MAH internal investigation, start January 2023, ongoing),
- POTS (MAH internal investigation, start 22 February 2023, ongoing),
- myocarditis/pericarditis (start February 2023, ongoing).

All ongoing signals except myo/pericarditis, which has been assessed in variation (EMEA/H/C/005737/II/072/G), should be presented in the next PSUR. During the reporting period, the safety concerns in the RMP were re-evaluated, i.e., the cRMP version 5.0 was updated to version 6.0 on 25 October 2022 with the reclassification of important potential risk of venous thromboembolism to an important identified risk.

After the DLP of this PSUR, a warning regarding myocarditis and pericarditis has been included in the US fact sheet. In a letter from the MAH to the EMA dated 31 March 2023, the MAH concludes that the available safety data supports a reasonable possibility of a causal association between Ad26.COV2.S and myocarditis and pericarditis. In the cover letter to this PBRER, the MAH confirms that in line with the request to submit a Type II variation to address myo-/pericarditis as an important identified risk for

JCOVDEN by 17 April 2023, the MAH has submitted a variation, including updated EU-PI and EU-RMP version 6.2 on 14 April 2023 (EMEA/H/C/005737/II/072/G). The PRAC concluded on this variation at its May 2023 meeting, and CHMP issued an opinion towards the end of May 2023; with updates of sections 4.4 and 4.8 of the SmPC, subsequent changes of the PIL.

Assessment of the data within the current PSUSA does not alter the balance between benefits and risks, and thus the benefit/risk balance remains unchanged.

3. Recommendations

Based on the PRAC review of data on safety and efficacy, the PRAC considers that the risk-benefit balance of medicinal products containing COVID-19 vaccine (Ad26.COV2-S [recombinant]) (JCOVDEN) remains unchanged and therefore recommends the maintenance of the marketing authorisation(s).

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

None

5. PSUR frequency

☒No changes to the PSUR frequency

The current **1-year** frequency for the submission of PSURs should remain unchanged.

Annex: preliminary 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 August 2022 to 24 February 2023. This is the fourth Periodic Safety Update-Single AR for JNJ-78436735(Ad26.COV2.S).

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

Ad26.COV2.S is a monovalent vaccine composed of a recombinant, replication-incompetent adenovirus type 26 vector, constructed to encode the severe acute respiratory syndrome coronavirus-2 spike protein. Following vaccination, the spike protein is expressed and stimulates an immune response.

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

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

1.2. Worldwide marketing authorisation status

Worldwide Marketing Authorisation Status
The International Birth Date (IBD) of Ad26.COV2.S is based on the first regulatory approval in Bahrain on 25 February 2021. Ad26.COV2.S is authorised in 104 countries/territories and import licences have been granted in 20 countries/territories worldwide. In addition, Ad26.COV2.S obtained an Emergency Use Listing by the World Health Organization.

Table 1: List of Countries/Territories Where Ad26.COV2.S is Authorised (n=104)

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

Key: n=Number

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

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

Key: n=Number

Rapporteur assessment comment:

The IBD of Ad26.COV2.S is based on the first regulatory approval in Bahrain on 25 February. In the EU Ad26.COV2.S was authorized on 11/03/2021. AD26.COV2.S is authorised in total 104 countries/territories worldwide and thus in 4 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 Period

Date	Country/Territory	Issue	Action Taken
23 December 2022	France	ANSM request to continue receiving information about pregnancy/breastfeeding cases with fatal outcome which occurred in France with Janssen COVID-19 vaccine.	The National PV Monitoring was re-opened regarding the pregnancy and breastfeeding cases with fatal outcome which occurred in France with the Janssen COVID-19 vaccine.
14 February 2023	United States	Externally identified significant safety issue.	US FDA requested an update to the Janssen COVID-19 vaccine EUA fact sheet to include a new Warnings and Precautions for myocarditis and pericarditis. HA notifications in other countries/territories were made in line with local requirements.

Key: ANSM=Agence Nationale de Sécurité du Médicament et des Produits de Santé; COVID-19=Coronavirus Disease 2019; EUA=Emergency Use Authorisation; FDA=Food and Drug Administration; HA=Health Authority; PV=Pharmacovigilance; US=United States

Rapporteur assessment comment:

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

1.3.2. Changes to reference safety information

The CCDS contains the Company Core Safety Information (CCSI). The CCDS in effect at the end of the reporting period is dated June 2022. No significant changes were made to the CCDS (ie, CCSI) within the reporting interval.

Rapporteur assessment comment:

No significant changes to the CCDS were made in the reporting interval.

Changes of the product information have been made during this PSUR period in the frame of procedure II/0064 to introduce an heterologous booster with Ad26.COV2.S following primary vaccination with another adenoviral vector-based vaccine and to provide updated follow-up data from studies which were included in variation EMEA/H/C/005737/II/0033. As a consequence, section 4.2, 4.8 and 5.1 of the SmPC have been updated. The PL has been updated accordingly.

Furthermore, ADR frequencies listed in section 4.8 were updated in the frame of procedure II/0060.

1.3.3. Estimated exposure and use patterns

Cumulative subject exposure in clinical trials

Overall, an estimated 82,249 healthy subjects have been enroled in the Ad26.COV2.S clinical programme, of which approximately 68,714 subjects received Ad26.COV2.S in the Company-sponsored interventional clinical trials (see Table 4). Of these, 675subjects were exposed to Ad26.COV2.S in the Phase 1 trials,5 935 subjects to Ad26.COV2.S in a Phase 1/2a trial,6 1,883 subjects to Ad26.COV2.S in the Phase 2 trials,7 537 subjects to Ad26.COV2.S in the Phase 2a trial,8 and over 64,684subjects 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,10 and 752,163 subjects to Ad26.COV2.S in the other studies.

Table 4: Estimated Cumulative Subject Exposure From Clinical Trials

Treatment	Number of Subjects
Ad26.COV2.S	68,714
Comparator	N/A
Placebo	39,413

Key: Ad26.COV2.S=Adenovirus type 26.Coronavirus 2.Spike; N/A=Not Applicable

Note: Number of subjects exposed to at least 1 study vaccine, recorded in the study databases up to cut-off date (24 February 2023).

Trials included: VAC31518COV1001, VAC31518COV1002, VAC31518COV1003, VAC31518COV2001, VAC31518COV2004, VAC31518COV2008, VAC31518COV3001, VAC31518COV3003, VAC31518COV3005, VAC31518COV3006, VAC31518COV3009, and VAC18193RSV2008.

The number of subjects exposed to study vaccine in blinded study (Ad26.COV2.S for VAC18193RSV2008) are estimates.

A total of 25,878 subjects (506 subjects from Trial VAC31518COV1001; 0 subjects from Trial VAC31518COV1002; 0 subjects from Trial VAC31518COV1003; 150 subjects from Trial VAC31518COV2001; 0 subjects from Trial VAC31518COV2004; 0 subjects from Trial VAC31518COV2008; 16,047 subjects from Trial VAC31518COV3001; 0 subjects from Trial VAC31518COV3003; 781 subjects from Trial VAC31518COV3005; 151 subjects from Trial VAC31518COV3006; 8,243 subjects from Trial VAC31518COV3009; and 0 subjects from Trial VAC18193RSV2008) that received a regimen with both Ad26.COV2.S and placebo, subjects are counted for both Ad26.COV2.S and placebo.

Cumulative and interval patient exposure from marketing experience

Post-approval (non-clinical trial) Exposure

Estimates of exposure are based on the number of delivered doses reported from LYNX Finance and administered doses reported from Centers for Disease Control and Prevention (CDC 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, Ministerio da Saude (Ministerio da Saude 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

The interval subject exposure for the Ad26.COV2.S vaccine during the reporting period (01 September 2022 to 28 February 2023) is provided in Table 7.

Table 7: Subject Exposure to the Ad26.COV2.S Vaccine During the Reporting Period (01 September 2022 to 28 February 2023)

Region/Country/Territory	Number of Distributed Doses[a]	Number of Administered Doses[b,c]
EEA		
Austria	0	443
Belgium	0	854
Bulgaria	0	4,167
Croatia	825,600	605
Cyprus	48,000	89
Czechia	0	844
Estonia	0	418
France	0	1,764
Germany	0	3,460
Greece	0	2,639
Hungary	0	3,727
Iceland	0	20
Ireland	0	4,549
Italy	0	867
Latvia	0	16,563
Lithuania	0	179
Malta	110,400	23
Norway	0	74
Poland	0	67,734
Portugal	0	2,528
Romania	0	3,837
Slovakia	0	1,406
Spain	0	874
ROW		
Afghanistan	2,901,600	NR
Algeria	223,200	NR
Cameroon	1,058,400	NR
Central African Republic	1,058,400	NR
Chad	2,570,400	NR
Congo, (Kinshasa)	14,332,800	NR
Côte D'ivoire	501,600	NR
Djibouti	86,400	NR
Gambia	230,400	NR
Ghana	1,051,200	NR
Grenada	2,400	NR
Guinea	1,514,400	NR
Guinea-Bissau	230,400	NR
Haiti	122,400	NR
Kenya	199,200	NR
Lesotho	439,200	NR
Liberia	79,200	NR
Madagascar	1,252,800	NR
Malawi	2,345,600	NR
Mali	1,881,550	NR
Mauritania	201,600	NR
Namibia	26,400	NR
Niger	2,268,000	NR
Nigeria	26,006,400	NR
Saint Lucia	4,800	NR
Saint Vincent and Grenadines	7,200	NR
Senegal	451,200	NR
Sierra Leone	1,370,400	NR

Table 7: Subject Exposure to the Ad26.COV2.S Vaccine During the Reporting Period (01 September 2022 to 28 February 2023)

Region/Country/Territory	Number of Distributed Doses[a]	Number of Administered Doses[b,c]
South Africa	11,376,000	139,858
South Korea	0	1,511
South Sudan	3,069,600	NR
Sudan	10,584,000	NR
Uganda	7,567,200	NR
Ukraine	1,101,600	NR
United Republic of Tanzania	19,936,750	NR
Uzbekistan	1,003,150	NR
Zambia	2,524,700	NR
US	***0***	***107,660***
Total	**120,564,550**	**366,693**

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 28 February 2023.

Cumulative Exposure Estimates

The cumulative subject exposure for the Ad26.COV2.S vaccine from launch to 28 February 2023 is provided in Table 8.

Table 8: Cumulative Subject Exposure to the Ad26.COV2.S Vaccine (Launch to 28 February 2023)

Region/Country/Territory	Number of Distributed Doses[a]	Number of Administered Doses[b,c]
EEA		
Austria	1,292,400	368,393
Belgium	629,200	428,570
Bulgaria	1,777,300	530,431
Croatia	1,135,150	204,713
Cyprus	190,500	31,033
Czechia	547,200	413,752
Denmark	1,198,800	46,004
Estonia	110,800	79,350
Finland	68,400	NR
France	3,416,300	1,090,592
Germany	7,818,150	3,753,219
Greece	1,521,600	786,023
Hungary	4,309,200	345,528
Iceland[d]	33,500	54,323
Ireland	281,500	241,646
Italy	2,370,000	1,483,503
Latvia	767,800	294,214
Liechtenstein	NR	264
Lithuania[d]	287,200	295,937
Luxembourg	80,200	41,489
Malta	226,800	32,421
Netherlands	2,464,800	755,524
Norway	403,900	7,399
Poland	15,523,300	2,984,415
Portugal[d]	993,600	1,139,518
Romania	4,080,300	2,068,803
Slovakia	475,200	186,591
Slovenia	230,400	135,699
Spain	2,659,000	1,981,696
Sweden	55,200	NR
ROW		
Afghanistan	17,596,850	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	4,057,250	NR
Burundi	302,400	NR
Cambodia	1,060,100	NR
Cameroon	4,800,650	NR
Canada	168,000	NR
Central African Republic	3,074,700	NR
Chad	10,364,050	NR
Colombia	11,504,800	NR
Congo (Brazzaville)	2,696,600	NR
Congo, (Kinshasa)	22,965,600	NR
Côte D'ivoire	5,774,200	NR

Table 8: Cumulative Subject Exposure to the Ad26.COV2.S Vaccine (Launch to 28 February 2023)

Region/Country/Territory	Number of Distributed Doses[a]	Number of Administered Doses[b,c]
Djibouti	446,400	NR
Egypt	15,513,450	NR
Ethiopia	41,759,750	NR
Gabon	866,400	NR
Gambia	777,600	NR
Ghana	9,840,000	NR
Grenada	2,400	NR
Guinea	2,594,400	NR
Guinea-Bissau	1,598,400	NR
Guyana	96,000	NR
Haiti	348,000	NR
Jamaica	216,000	NR
Kenya	14,944,250	NR
Lao PDR	1,771,200	NR
Lebanon	336,000	NR
Lesotho	1,472,250	NR
Liberia	3,211,200	NR
Madagascar	4,790,750	NR
Malawi	5,913,950	NR
Mali	3,333,550	NR
Mauritania	2,484,000	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	5,738,400	NR
Nigeria	75,009,250	NR
Papua New Guinea	820,800	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	2,190,300	NR
Sierra Leone	4,248,000	NR
Solomon Islands	100,800	NR
South Africa	30,999,200	7,945,607
South Korea	3,411,000	1,516,527
South Sudan	5,862,650	NR
Sudan	17,312,300	NR
Swaziland	302,400	NR
Switzerland	200	NR
Syrian Arab Republic (Syria)	3,458,400	NR
Togo	2,620,800	NR
Trinidad and Tobago	259,200	NR
Tunisia	1,540,800	NR
Turkey	832,800	NR
Uganda	23,388,000	NR
Ukraine	1,202,400	NR
United Republic of Tanzania	34,890,150	NR
Uzbekistan	1,003,150	NR
Vanuatu	43,150	NR
Yemen	1,197,600	NR
Zambia	12,367,050	NR
US	***41,225,650[e]***	***18,982,882***
Total	**611,193,650[f]**	**53,047,996**

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 the EEA countries/territories, from the KDCA for South Korea, from the Ministério da Saúde for Brazil, and from the NDH for South Africa. The data for administered doses for Brazil was last updated by the Ministério da Saúde website on 15 November 2021, and for Germany, the data for administered doses was last updated by the 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 28 February 2023.

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.

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 9.

Table 9: Total Number of Subjects With the Homologous Ad26.COV2.S Vaccine Booster Doses

Country/Territory	Interval	Cumulative
South Africa	133,775	1,520,478
South Korea[a]	8	27,032
US[b]	19,013	1,585,122
Total	**152,796**	**3,132,632**

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

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

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

Exposure by Age for Ad26.COV2.S in EEA

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

Post-authorisation use in special populations

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

Other Post-approval Use

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

Rapporteur assessment comment:

A total of 120,564,550 doses12 of Ad26.COV2.S vaccine were distributed worldwide from 01 September 2022 to 28 February 2023. In the current reporting period, there has been an approximately 6%decrease in distributed doses worldwide compared to the previous reporting period (01 March 2022 to 31 August 2022; 123,582,300 dosages). A total of 366,693 doses of Ad26.COV2.S vaccine were administered worldwide from 01 September 2022 to 28 February 2023. In the current reporting period, there has been an approximately 62%decrease in administered doses worldwide compared to the previous reporting period (01 March 2022 to 31 August 2022). In the EU the largest number of administered doses was in Poland (67,734) and Latvia (16,563). The distribution and administration of Ad26.COV2.S vaccine in EEA countries decreased further during the current interval.

A total of 611,193,650 doses of Ad26.COV2.S vaccine were distributed worldwide from launch to 28 February 2023. A total of 53,047,996 doses of Ad26.COV2.S vaccine were administered worldwide from launch to 28 February 2023.

1.3.4. Data in summary tabulations

Appendix 2.1.1 and Appendix 2.1.2 of the MAH report contain a cumulative tabulation of serious adverse event(s) (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.

Appendix 2.2 of the MAH report contains cumulative and interval summary tabulations of "suspected adverse reactions" (thereafter called "adverse reactions" [ARs]) received cumulatively to the DLD of this PBRER. These ARs are derived from non-interventional post-marketing studies, other solicited sources and spontaneous notification, including reports from healthcare professionals, consumers, scientific literature, and regulatory authorities. Appendix 2.2 also displays ARs from special situation cases (eg, pregnancy, off-label use, overdose, medication error) with no additional ARs reported.

Rapporteur assessment comment:

During the reporting period, 7,626 serious ARs and 14,821 nonserious ARs were received from spontaneous sources, and 98 serious ARs were received from non-interventional post-marketing studies and other solicited sources. From spontaneous sources, non-interventional post-marketing studies, and other solicited sources, the SOCs including the most reported ARs were:

☐ General Disorders and Administration Site Conditions (7,439)

☐ Nervous System Disorders (3,529)

☐ Musculoskeletal and Connective Tissue Disorders (2,182)

☐ Infections and Infestations (1,680)

☐ Investigations (1,357)

Cumulatively, 99,521 serious ARs (98,343 spontaneous, 1,178 from non-interventional post-marketing studies and other solicited sources) were received by the Marketing Authorisation Holder (MAH). No new important safety information is identified.

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 DLP for this PBRER reporting period. During the PBRER reporting period, 2 Company-sponsored interventional clinical trials (VAC31518COV1002 and VAC31518COV1003) of Ad26.COV2.S were completed. These clinical trials are briefly summarised below:

Trial VAC31518COV1002

This was a Phase 1, randomised, double-blind, placebo-controlled trial in healthy adults aged ≥20 to ≤55years and ≥65 years in good health with or without stable underlying conditions in Japan to evaluate the safety, reactogenicity, and immunogenicity of Ad26.COV2.S at 2 dose levels, administered IM as 2-dose schedule.

Safety Summary

The safety data regarding deaths, other serious or significant AEs for Cohort 1 and Cohort 2 are described below.

Cohort 1:

Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

There were no deaths in Cohort 1. An SAE of sudden hearing loss (Grade 4) was reported in 1 participant from the 5×1010, 5×1010 vp group during post-dose 1 follow-up. One participant from the 1×1011,

1×1011 vp group experienced an AE of blood pressure increased (Grade 3) during post-dose 1 follow-up and resulted in study vaccine discontinuation. Both events resolved during their time on the study and were considered not related to the study vaccine by the investigator. No Adverse Event of Special Interest (AESI) and suspected AESI were reported.

Cohort 2

Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

One death was reported in Cohort 2. The cause of the death was acute myocardial infarction and was considered as not related to the study vaccine by the investigator. A total of 6 participants reported the following SAEs: schwannoma, embolic stroke, intervertebral disc protrusion, acute myocardial infarction, cystocele and uterine prolapse, and constipation (all SAEs reported at Grade 4). None of these SAEs were considered as related to the study vaccine by the investigator. From the time of local approval of protocol Amendment 5 onwards (8 June 2021), Thrombosis with Thrombocytopenia Syndrome (TTS) was considered to be an AESI. Suspected AESIs (thrombotic events and/or thrombocytopenia [defined as platelet count below 15×104/µL]) were recorded from the moment of vaccination until the end of the trial/early withdrawal. An AESI Adjudication Committee with appropriate expertise was established to evaluate each suspected AESI and determine whether it is a case ofTTS. Three participants reported the following suspected AESIs: embolic stroke (Grade 4), acute myocardial infarction (Grade 4), and thrombocytopenia (Grade 2). Embolic stroke and thrombocytopenia were not considered a case of TTS by the AESI adjudication committee. Only acute myocardial infarction event was assessed as a case of TTS by the committee, Brighton Collaboration level 3 (Brighton Collaboration 2021), CDC criteria "non Tier-1" (Shimabukuro 2021). None of these suspected AESIs were considered as related to the study vaccine by the investigator.

Trial VAC31518COV1003

This was a Phase 1, randomised, observer-blind, parallel-group trial to compare the safety, reactogenicity, and immunogenicity ofAd26.COV2.S at a single-dose of 5×1010 vp in 2 different volumes (0.3 mL and 0.5 mL) in healthy adults aged ≥18 to ≤65years. Overall, in conclusion, no safety issues were identified in adult participants after receiving the Ad26.COV2.S vaccine at a single dose of 5×1010 vp in a test volume of 0.3 mL. The safety and reactogenicity profile were in line with that of the authorised 0.5 mL presentations. No fatal AEs, AESIs, or AEs leading to study discontinuation were reported. Serious AEs were reported for 1 participant in the 0.3-mL vaccination group and 1 participant in the 0.5-mL vaccination group during the follow-up phase. All SAEs were considered to be not related to the study vaccine by the investigator.

1.3.5.2. Ongoing clinical trials

An "ongoing clinical trial" is defined as a trial for which the first informed consent form has been signed, but for which a final CSR is not available at the data-lock point for this PBRER reporting period, regardless of whether the last subject last visit has occurred. During the PBRER reporting period, 9 Company-sponsored, interventional clinical trials (VAC31518COV1001, VAC31518COV2004, VAC31518COV2008, VAC31518COV3001, VAC31518COV3003, VAC31518COV3005, VAC31518COV3006, VAC31518COV3009, and VAC18193RSV2008) ofAd26.COV2.S were ongoing. Of these 9 clinical trials, 1 clinical trial (VAC18193RSV2008) was initiated during the PBRER reporting period. These clinical trials are briefly summarised below:

☐ **Trial VAC31518COV1001:** This is a Phase 1/2a, randomised, double-blind, placebo-controlled, first-in-human, multicentre trial in healthy adults aged ≥18 to ≤55years and aged ≥65years in good health with or without stable underlying conditions to evaluate the safety,

reactogenicity, and immunogenicity of Ad26.COV2.S at 2-dose levels, administered IM as a single-dose or 2-dose schedule, with a single booster vaccination administered in 1 cohort. An ad hoc booster vaccination with Ad26.COV2.S will be provided in open-label fashion to eligible participants who have previously received 1 or more doses of any COVID-19 vaccine, if the last vaccination was ≥6 months ago. No significant safety findings were identified from this trial during the reporting period.

☐ **Trial VAC31518COV2004:** This is a Phase 2, open-label, multicentre trial to evaluate the safety, reactogenicity, 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 naive at study entry. No significant safety findings were identified from this trial during the reporting period.

☐ **Trial VAC31518COV2008:** This is a Phase 2, randomised, double-blind, parallel, multicentre trial to evaluate the immunogenicity, reactogenicity, and safety of Ad26.COV2.S administered as a 1-dose booster vaccination (5×1010 vp or 2.5×1010 vp or 1×1010 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).
No significant safety findings were identified from this trial during the reporting period.

☐ **Trial VAC31518COV3001:** This is a Phase 3, randomised, double-blind, placebo-controlled, multicentre, pivotal efficacy, and safety trial in adults ≥18 years of age. The efficacy, safety, and immunogenicity of Ad26.COV2.S is evaluated in participants living in, or going to, locationswith high risk for acquisition of SARS-CoV-2 infection after administration of study vaccine. All participants who initially received placebo in the double-blind phase were offered a single dose of Ad26.COV2.S vaccine 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. No significant safety findings were identified from this trial during the reporting period.

☐ **Trial VAC31518COV3003:** This is a Phase 3, randomised, double-blind trial to evaluate 6 dose levels of Ad26.COV2.S administered as a 2-dose schedule in healthy adults aged 18 to 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 55years will be enroled (into study groups 1, 3, 5, and 6) to further characterise the innate, pro-inflammatory, and other relevant (eg, pro-thrombotic) responses to Ad26.COV2.S to better understand a possible risk to TTS events. No significant safety findings were identified from this trial during the reporting period.

☐ **Trial VAC31518COV3005:** This is a Phase 3, randomised, double-blind, parallel, multicentre trial 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 ≤64years) 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. No significant safety findings were identified from this trial during the reporting period.

☐ **Trial VAC31518COV3006:** This is a Phase 2, randomised, observer-blind, pivotal 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. No significant safety findings were identified from this trial during the reporting period.

☐ **Trial VAC31518COV3009:** This is a Phase 3, randomised, double-blind, placebo-controlled, multicentre, pivotal efficacy and safety trial in adults ≥18 years of age. The efficacy, safety, and immunogenicity of Ad26.COV2.S is 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 and participants are in long-term follow-up for safety. No significant safety findings were identified from this trial during the reporting period.

☐ **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 vaccine 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 period.

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

Long-term Follow-up
During the reporting period, no long-term follow-up information for Ad26.COV2.S became available.

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 period.

New Safety Data Related to Fixed Combination Therapies
Ad26.COV2.S is currently not under development as a fixed-dose combination or multidrug regimen.

Rapporteur assessment comment:

During the PBRER reporting period, 2 Company-sponsored interventional clinical trials (VAC31518COV1002 and VAC31518COV1003) of Ad26.COV2.S were completed. Furthermore, during the PBRER reporting period, 9 Company-sponsored, interventional clinical trials (VAC31518COV1001, VAC31518COV2004, VAC31518COV2008, VAC31518COV3001, VAC31518COV3003, VAC31518COV3005, VAC31518COV3006, VAC31518COV3009, and VAC18193RSV2008) ofAd26.COV2.S were ongoing. Of these 9 clinical trials, 1 clinical trial (VAC18193RSV2008) was initiated during the PBRER reporting period.

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

FINDINGS FROM NON-INTERVENTIONAL STUDIES
Based on review of the data from noninterventional study for Ad26.COV2.S during the PBRER reporting period, no new information with potential impact to the benefit-risk assessment has been identified. Summary from Real World Evidence (RWE) studies is presented below.

Real World Evidence Summary for Ad26.COV2.S

The Company-sponsored (VAC31518COV4004 and VAC31518COV4019), collaborative, and publicly available RWE studies reporting on the vaccine effectiveness of Ad26.COV2.S are described below:

Study VAC31518COV4004
Interim results for the primary objective were available for Study VAC31518COV4004, multi-centre, multi-country, hospital-based case-control study with Test-Negative Control (TNCC) 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. The interim results from Janssen's multi-country TNCC study (VAC31518COV4004) through July 2022 demonstrated that a single-dose of Ad26.COV2.S provided protection against laboratory confirmed SARS-CoV-2 SARI hospitalisations.

Study VAC31518COV4019
Interim results were available from Study VAC31518COV4019, 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], messenger Ribonucleic Acid (mRNA;1273 [2 doses]) using both open and closed-claims data elements aggregated by Health Verity. Both homologous and heterologous booster vaccines provided protection against COVID-19 related hospitalisations for up to 6 months.

There have been other RWE studies that have been recently published by researchers, that evaluate the vaccine effectiveness (VE) of single dose and booster Ad26.COV2.S vaccine. The protection against COVID-19 varies between different variants of concern (VOC)s. These literatures appear to confirm 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:
Several studies using RWE are performed by the MAH to study the vaccine effectiveness. The effectiveness has been dependent on the different circulating variants of SARS-CoV-2. No new safety concern is detected here.

1.3.5.3. Other Clinical Trials

During the PBRER reporting period, 8 interventional clinical trials sponsored by other organisations/institutions were ongoing The summary and safety findings from these trials are presented below.

Trial COV-BOOST (VAC31518COV2009)
This is a Phase 2, randomised, multicentre trial conducting in the United Kingdom (UK) to determine reactogenicity and immunogenicity of booster vaccination against ancestral and novel variants of SARS-CoV-2. The trial will initially consist of several cohorts enrolled in 2 or 3 stages.
At the time of DLP of this PBRER, 2,878 participants were enroled, of which 206 received Ad26.COV2.S. During the reporting period, no significant safety information related to Ad26.COV2.S from this clinical trial became available.

Trial VAC31518COV2012
This is Phase 1/2, prospective, multicentre, observer-blind adaptive trial to assess the safety, reactogenicity, and immunogenicity of a booster dose of Ad26.COV2.S in adults ≥18 years of age in trial

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 DLP of this PBRER, 478 participants received Ad26.COV2.S in this trial. During the reporting period, no new significant safety findings related to Ad26.COV2.S from this clinical trial became available.

Trial VAC31518COV2016 (AUR1-8-341)
This is a Phase 2a, randomised, observer-blind, multicentre trial of the safety and immunogenicity ofCOVID-19 vaccine strategies in Human Immunodeficiency Virus (HIV)-infected and HIV-uninfected adults. A total of 750 evaluable HIV-infected (660) and HIV-uninfected (90) adult participants meeting all entry criteria (all inclusion and no exclusion criteria) will be enroled in 3 treatment strategies in 3 participant groups dependent on prior vaccination with a single-dose of Janssen (Group 1), 2 doses of Pfizer (Group 2), or no prior COVID-19 vaccination with evidence of prior SARS-CoV-2 infection (Group 3).
At the time of DLP of this PBRER, 231 participants received Ad26.COV2.S in this trial. During the reporting period, no new significant safety findings related to Ad26.COV2.S from this clinical trial became available.

Trial VAC31518COV3012 (Sisonke [Together])
This is a Phase 3b, open-label, single-arm, multicentre, implementation trial to monitor the effectiveness of the single-dose of Ad26.COV2.S among Health Care Workers (HCW) at least 18 years of age as compared with the general unvaccinated population in South Africa. All HCWs who register on the National Vaccination Registry were eligible for enrolment. At the time of DLP of this PBRER, 499,887 participants received Ad26.COV2.S in this trial.
During the reporting period, no new significant safety findings related to Ad26.COV2.S from this clinical trial became available.

Trial VAC31518COV3018
This is a Phase 3, prospective, open-label clinical trial with 1 randomised arm to evaluate the response of a heterologous additional dose with the Janssen Ad26.CoV2.S vaccine to provide vaccine induced immunity for immunocompromised kidney transplant patients after receiving 2 or more doses of the Pfizer or Moderna COVID-19 vaccine.
At the time of DLP of this PBRER, 35 participants received Ad26.COV2.S in this trial. During the reporting period, no new significant safety findings related to Ad26.COV2.S from this clinical trial became available.

Trial VAC31518COV3021 (Sisonke Boost Open-label Study [SISONKE2])
This is a Phase 3b, open-label, single-arm, multicentre, implementation trial in Sisonke participants in South Africa at least 18 years of age. This trial will be conducted by Sisonke (VAC31518COV3012) sites in collaboration (where appropriate) with routine National Department of Health vaccination centres in South Africa. All Sisonke participants registered on the National Vaccination Registry were eligible for enrolment, if eligibility is met.
At the time of DLP of this PBRER, 250,878 participants received Ad26.COV2.S in this trial. During the reporting period, no new significant safety findings related to Ad26.COV2.S from this clinical trial became available.

Trial VAC31518COV4012
This is a trial 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 the Ad26.COV2.S vaccine and

boosting with either Ad26.COV2.S vaccine 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 vaccine and boosting with either Ad26.COV2.S vaccine or mRNA vaccines.
At the time of DLP of this PBRER, 298 participants received Ad26.COV2.S in this trial.
During the reporting period, no new significant safety findings related to Ad26.COV2.S from this clinical trial became available.

Trial DMID 21-0012
This is a Phase 1/2, open-label trial 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 trial is designed to assess the safety, reactogenicity, and immunogenicity of a delayed (>12 weeks) vaccine boost on a range of Emergency Use Authorisation-dosed COVID-19 vaccines (mRNA-1273 manufactured by ModernaTX, Inc.; BNT162b2 manufactured by Pfizer/BioNTech; or Ad26.COV2.S manufactured by Janssen Pharmaceuticals/Johnson & Johnson).
At the time of DLP of this PBRER, 150 participants received Ad26.COV2.S in this trial.
During the reporting period, no significant safety information related to Ad26.COV2.S from this clinical trial became available.

Rapporteur assessment comment: Several studies are ongoing. Overall, no new safety findings were identified during the reporting period from these.

9.2. Medication Errors
Results/Discussion

During this reporting period, a total of 49 (44medically confirmed and 5medically unconfirmed) initial, primary dose cases reporting medication errors were retrieved. There were 6 serious and 43 nonserious cases which reported a total of 63 medication error events (5 serious, 58 nonserious).

During this reporting period, a total of 11 (3 medically confirmed and 8 medically unconfirmed) cases reported as booster were identified. There were 10 serious and 1 nonserious case, which reported a total of 11 medication error events (4serious, 7 nonserious). All 11 cases were heterologous.

Post-marketing Sources (Including Spontaneous and Solicited) Cases

Primary Dose

During this reporting period, a total of 46 (41 medically confirmed and 5 medically unconfirmed) post-marketing, initial, primary dose cases reporting medication errors were retrieved. Of these 46 cases, 1 concerned a paediatric patient which is discussed in subsection "Paediatric Cases" below. The remaining 45 cases reported 59 medication error events (3 serious, 56 nonserious) and are presented below.

Cumulatively, 2,505 (1,785 medically confirmed and 720 medically unconfirmed) post-marketing, primary dose cases reporting medication errors were retrieved. Of these 2,505cases, 372 concerned paediatric patients which are discussed in subsection 9.2.1, Paediatric Cases below. The remaining 2,133 cases reported a total of 2,870 medication error events (35 serious; 2,835nonserious) and are presented below.

An overview of these cases is presented in Table 10 below.

Table 10: Characteristics of Selected Post-marketing Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Medication Errors

Case Characteristics		Number of Cases Received During the Interval Reporting Period=45	Number of Cases Received Cumulatively=2,133[a]
Sex	Male	16	713
	Female	12	685
	NR	17	735
Age (Years)[b]	18 to 35	7	321
Minimum: 19	36 to 50	5	302
Maximum: 80	51 to 64	6	351
Mean: 45.4	≥65	3	186
Median: 48	NR	24	926
Source	Spontaneous	44	2,121
	Clinical study (noninterventional, solicited)	1	11
Country/Territory	United States	38	1,833
	France	2	74
	Austria	1	4
	Canada	1	9
	Colombia	1	6
	Ireland	1	12
	South Africa	1	4
Event Characteristics		**Number of Events=59**	**Number of Events=2,870**
Seriousness (Event Level)[c]	Nonserious	56	2,835
	Serious	3	35
Outcome (Event Level)[c]	Not resolved	1	35
	Resolved	1	49
	NR	57	2,779

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 period (25 August 2022 to 24 February 2023).
b: The median and mean age calculation were based on the current reporting period (25 August 2022 to 24 February 2023).
c: Seriousness and outcome have been presented for the events of interest. A single case may report more than 1 EOI.

The frequency distribution of the MedDRA PTs of interest reported in cases (n=45) is presented in Table 11 below.

Table 11: Frequency Distribution of MedDRA PTs in Post-marketing Primary Dose Cases Reporting Medication Errors With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
Expired product administered	0	26	4	539
Poor quality product administered	0	12	0	708
Product storage error	0	12	2	594
Product administered at inappropriate site	1	1	2	17
Device infusion issue	1	0	1	0
Inappropriate schedule of product administration	0	1	1	95
Interchange of vaccine products	1	0	2	7
Medication error	0	1	1	119
Product administration error	0	1	2	66
Product dispensing error	0	1	0	11
Product use issue	0	1	1	17

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: The MedDRA PTs of interest were sorted by decreasing order for the current reporting period (25 August 2022 to 24 February 2023). 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 period (25 August 2022 to 24 February 2023).

The majority (82.2%; 37/45) of the cases involved medication errors without any additional AEs reported (classified as error without harm); whereas 17.8% (8/45) of cases reported medication errors with harm. These 8 cases reported 47 additional events (36 serious, 11 nonserious). The most frequently reported events of medication errors in these cases (n≥2) were expired product administered and product administered at inappropriate site (n=2 each). The frequency distribution of additional AEs (n≥2) reported in 8 cases reporting medication errors with harm with the use of Ad26.COV2.S is presented in Table 12 below. Most of the serious AEs occurred in 2 patients who experienced rhabdomyolysis in association with either alcohol withdrawal syndrome or diabetic ketoacidosis caused by pump failure. Reported medication errors referred to interchange of vaccine products (second dose of unspecified vaccine at unspecified time after Ad26.COV2.S) and to device infusion issue, respectively.

Table 12: Frequency Distribution of Additional AEs in Post-marketing Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Medication Errors With Harm

Additional AEs	Number of Events Received During the Interval Reporting Period[a]		Number of Events Received Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
Anal incontinence	1	1	1	2
Confusional state	2	0	2	1
Pain	1	1	6	68
Rhabdomyolysis	2	0	2	0

Key: AE=Adverse Event

a: The AEs with a frequency ≥2 have been presented and sorted by decreasing order for the current reporting period (25 August 2022 to 24 February 2023). 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 period (25 August 2022 to 24 February 2023).

Booster Dose During this reporting period, a total of 11 (3 medically confirmed and 8 medically unconfirmed) post-marketing, initial cases reported as booster were identified. None of these 11 cases concerned paediatric patients. These 11 booster dose cases reported 11 medication error events (4serious, 7 nonserious) and are presented below. Cumulatively, 1,079 (280 medically confirmed and 799 medically unconfirmed) post-marketing cases reported as booster were identified. Of these 1,079 cases, 7 concerned paediatric patients which are discussed in the subsection Paediatric Cases. The remaining 1,072 booster dose cases reported a total of 1,110 mediation error events (19 serious; 1,091 nonserious) and are presented below.

An overview of these cases is presented in Table 13 below.

Table 13: Characteristics of Selected Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Medication Errors

Case Characteristics		Number of Cases Received During the Interval Reporting Period=11	Number of Cases Received Cumulatively=1,072[a]
Sex	Male	6	503
	Female	5	525
Age (Years)[b]	18 to 35	1	214
Minimum: 26	36 to 50	2	267
Maximum: 83	51 to 64	2	182
Mean: 55.3	≥65	2	154
Median: 55	NR	4	245
Source	Spontaneous	8	748
	Clinical study (noninterventional, solicited)	2	313
	Clinical study (noninterventional,	1	11

Table 13: Characteristics of Selected Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Medication Errors

Case Characteristics		Number of Cases Received During the Interval Reporting Period=11	Number of Cases Received Cumulatively=1,072[a]
	unsolicited)		
Country/Territory	Germany	5	29
	United States	4	458
	Brazil	2	423
Classification	Heterologous	11	392
Event Characteristics		**Number of Events=11**	**Number of Events=1,110**
Seriousness (Event Level)[c]	Nonserious	7	1,091
	Serious	4	19
Outcome (Event Level)[c]	Resolved	1	7
	NR	10	1,095

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 period (25 August 2022 to 24 February 2023).
b: The median and mean age calculations were based on the current reporting period (25 August 2022 to 24 February 2023).
c: Seriousness and outcome have been presented for the EOI.

Of these 11 post-marketing cases reported as booster received during the reporting period, the reported countries/territories of origin were Germany (n=5), the US (n=4), and Brazil (n=2). These cases concerned 6 males and 5females. The age range was from 26 to 83 years. The frequency distribution of the MedDRA PTs of interest reported in cases reported as booster is presented in Table 14below.

Table 14: Frequency Distribution of MedDRA PTs in Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Medication Errors

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
Interchange of vaccine products	4	4	16	12
Inappropriate schedule of product administration	0	3	0	879

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: The MedDRA PTs of interest are sorted by decreasing order for the current reporting period (25 August 2022 to 24 February 2023).
b: For the cumulative column, the events were presented in decreasing order based on the event counts of the current reporting period (25 August 2022 to 24 February 2023).

As displayed in Table 14, the most frequently reported MedDRA PTs of interest for this current reporting period was Interchange of vaccine products (n=8). Of the 11 cases reported as booster, the majority (90.9%; 10/11) of them contained additional AEs (classified as medication errors with harm). These 10 cases reported 65additional events (25serious, 40 nonserious). The reported events of medication errors in these cases were interchange of vaccine products (n=8) and inappropriate schedule of product administration (n=2). The frequency distribution of additional AEs (n≥2) reported in these 10 cases is presented in Table 15 below. Most of the frequently reported events were nonserious; and serious adverse events were reported in 10 patients, where the frequently reported adverse events were drug ineffective, gait inability and/or rheumatoid arthritis or COVID-19 infection.

Table 15: Frequency Distribution of Additional AEs in Post-marketing Cases Reported as Booster Involving Use of Ad26.COV2.S and Reporting Medication Errors With Harm

Additional AEs	Number of Events Received During the Interval Reporting Period[a]		Number of Events Received Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
Drug ineffective	3	0	8	0
COVID-19	1	1	7	22
Depression	0	2	0	3
Gait inability	1	1	1	5
Migraine	0	2	1	3
Palpitations	0	2	1	3
Rheumatoid arthritis	2	0	3	0
Suspected COVID-19	2	0	3	11

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

a: The AEs with a frequency ≥2 have been presented for the current reporting period (25 August 2022 to 24 February 2023). 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 period (25 August 2022 to 24 February 2023).

Paediatric Cases

Post-marketing Sources (Including Spontaneous and Solicited) Cases

Primary Dose

During this reporting period, a total of 1 medically confirmed (no medically unconfirmed) post-marketing, initial case reporting medication error in the paediatric population was retrieved. This spontaneous case concerned a 17-year-old male from [redacted] who experienced 1 nonserious event of product administered to patient of inappropriate age and an additional nonserious event of off label use, and hence the event of interest (EOI) did not represent a true medication error. No additional AEs were reported. Cumulatively, 372 (194 medically confirmed and 178 medically unconfirmed) post-marketing, primary dose cases reporting medication errors in the paediatric population were retrieved. There were 23 serious and 349 nonserious cases which reported a total of 401 medication error events (7 serious, 394nonserious).

Paediatric Booster Dose Cases

During this reporting period, 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 the paediatric population were identified. There were 1 serious and 6 nonserious cases which reported a total of 10 nonserious events of medication error.

Clinical Trial Cases

During this reporting period, a total of 3 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 period, 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 period, 1 primary dose with a reported medication error (incorrect vaccine administered without further information) and no booster cases were retrieved from a Janssen Supported Clinical Study.

Line Listings

Death: During the current reporting period (25August 2022 to 24February 2023), 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 dose 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 dose 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:

Medication errors with Ad26.COV2.S during the reporting period did not follow specific patterns suggestive for a new safety concern.

Only a very limited number of children vaccinated with Ad26.COV2.S has been reported. No new safety concern arises here.

Non-clinical data

During the period covered by this report, the following nonclinical studies continue to be conducted with focus on TTS and results are pending (see Table 16).

Table 16: Overview of Ongoing Nonclinical Study With Focus on TTS for JNJ-78436735 (Ad26.COV2.S)

Nonclinical Study Number	Nonclinical Study Title
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; TTS=Thrombosis with Thrombocytopenia Syndrome

Further, the following nonclinical studies were completed during this reporting period and the results are summarised in below (see Table 17).

Table 17: Overview of Completed Nonclinical Studies with Focus on TTS for JNJ-78436735 (Ad26.COV2.S)

Nonclinical Study Number	Nonclinical Study Title	Nonclinical Data
TV-TEC-236300	Biophysical investigations on interactions between human platelet factor 4 and Ad26.COV2.S	A possible interaction between PF4 and Ad26.COV2.S that has been hypothesised to lead to induction of anti-PF4 antibodies has been assessed using 3 different biophysical techniques: DLS, BLI, and SPR. In DLS and BLI experiments, no direct interactions between PF4 and Ad26.COV2.S were observed. SPR data demonstrated that the induced binding of PF4 to Ad26.COV2.S as published by Baker et al. (Baker 2021)[a] is likely an experimental artefact. These findings are in line with findings of Michalik et al. (Michalik 2022)[b] using DLS, showing no complex formation of PF4 with Ad26.COV2.S. Therefore, it is unlikely that binding of Ad26-vector particles to PF4 is driving the pathology of TTS.
TOX15155	VAC31518 SARS-COV-2 vaccine (COVID-19): Immunogenicity and biodistribution/protein expression study in New Zealand white rabbits	Expression of S protein was assessed in the IM administration site, draining lymph nodes, and spleen by immunohistochemistry and in the blood by S-PLEX assay, on Days 1 and 11 following IM dosing in rabbits. A transient expression of the S protein was observed in the IM administration site, draining lymph nodes (iliac and/or popliteal), and blood on Day 1, with all tissues examined being negative for S protein expression on Day 11 post dosing. No adverse vaccine-related effects were noted. Overall, Ad26.COV2.S-induced S protein expression, including its bioavailability in blood, was not associated with a safety concern in this study, but does not allow S protein to be ruled out as a potential contributing factor in a multifactorial scenario of TTS induction following vaccination with Ad26.COV2.S in humans.

Key: Ad26.COV2.S=Adenovirus Type 26 Coronavirus 2 Spike; BLI=Biolayer Interferometry; DLS=Dynamic Light Scattering; IM=Intramuscular; PF4=Platelet Factor 4; SPR=Surface Plasmon Resonance; TTS=Thrombosis with Thrombocytopenia Syndrome

a: Baker AT, Boyd RJ, Sarkar D, et al. ChAdOx1 interacts with CAR and PF4 with implications for thrombosis with thrombocytopenia syndrome. Sci Adv. 2021; 7(49):(eabl8213).

b: Michalik S, Siegerist F, Palankar E, et al. Comparative analysis of ChAdOx1 nCoV-19 and Ad26.COV2.S SARS CoV-2 vector vaccines. Haematologica. 2022;107(4):947-957.

The available (mechanistic) nonclinical data generated with Ad26.COV2.S do not allow to conclude on the potential mechanism of TTS. No new safety concerns were identified from nonclinical studies.

Rapporteur assessment comment:

1.3.5.4. One ongoing and two finalised non-clinical studies focusing on TTS were shortly described in the PSUSA. No further insight in the mechanism behind TTS is apparent from these studies. Literature

Product-Specific Literature

Gibson EA, Li H, Fruh V, et al. COVID-19 Vaccination and Menstrual Cycle Length in the Apple Women's Health Study. *MedRxiv.* 2023.

COVID-19 vaccination may be associated with change in menstrual cycle length following vaccination.

Methods: We conducted a longitudinal analysis within a subgroup of 14,915 participants in the Apple Women's Health Study (AWHS) who enrolled between November 2019 and December 2021 and met the following eligibility criteria: were living in the US, met minimum age requirements for consent, were English speaking, actively tracked their menstrual cycles, and responded to the COVID-19 Vaccine Update survey. In the main analysis, we included tracked cycles recorded when premenopausal participants were not pregnant, lactating, or using hormonal contraceptives. We used conditional linear regression and multivariable linear mixed-effects models with random intercepts to estimate the covariate-adjusted difference in mean cycle length, measured in days, between pre-vaccination cycles, cycles in which a vaccine was administered, and post-vaccination cycles within vaccinated participants, and between vaccinated and unvaccinated participants. We further compared associations between vaccination and menstrual cycle length by the timing of vaccine dose within a menstrual cycle (i.e., in follicular or luteal phase). We present Bonferroni-adjusted 95% confidence intervals (CI) to account for multiple comparisons.

Results: A total of 128,094 cycles (median=10 cycles per participant; interquartile range: 4 to 22) from 9,652 participants (8,486 vaccinated; 1,166 unvaccinated) were included. The average within-individual standard deviation in cycle length was 4.2 days. Fifty-five percent of vaccinated participants received Pfizer-BioNTech's mRNA vaccine, 37%

received Moderna's mRNA vaccine, and 7% received the Johnson & Johnson/Janssen vaccine (J&J). We found no evidence of a difference between mean menstrual cycle length in the unvaccinated and vaccinated participants prior to vaccination (0.24 days, 95% CI: -0.34, 0.82). Among vaccinated participants, COVID-19 vaccination was associated with a small increase in mean cycle length (MCL) for cycles in which participants received the first dose (0.50 days, 95% CI: 0.22, 0.78) and cycles in which participants received the second dose (0.39 days, 95% CI: 0.11, 0.67) of mRNA vaccines compared with pre-vaccination cycles. Cycles in which the single dose of J&J was administered were, on average, 1.26 days longer (95% CI: 0.45, 2.07) than pre-vaccination cycles. Post-vaccination cycles returned to average pre-vaccination length. Estimates for pre vs post cycle lengths were 0.14 days (95% CI: -0.13, 0.40) in the first cycle following vaccination, 0.13 days (95% CI: -0.14, 0.40) in the second, -0.17 days (95% CI: -0.43, 0.10) in the third, and -0.25 days (95% CI: -0.52, 0.01) in the fourth cycle post-vaccination. Follicular phase vaccination was associated with an increase in MCL in cycles in which participants received the first dose (0.97 days, 95% CI: 0.53, 1.42) or the second dose (1.43 days, 95% CI: 1.06, 1.80) of mRNA vaccines or the J&J dose (2.27 days, 95% CI: 1.04, 3.50), compared with pre-vaccination cycles.
Conclusion: COVID-19 vaccination was associated with an immediate short-term increase in menstrual cycle length overall, which appeared to be driven by doses received in the follicular phase. However, the magnitude of this increase was small and diminished in each cycle following vaccination. No association with cycle length persisted over time. The magnitude of change associated with vaccination was well within the natural variability in the study population. Menstrual cycle change following COVID-19 vaccination appears small and temporary and should not discourage individuals from becoming vaccinated.
***MAH Comments*:** The article presents, "*the relationship between COVID-19 vaccination and menstrual cycle length over time in the AWHS, a longitudinal digital cohort of people in the U.S. with manually tracked menstrual cycles". It "compare[s] pre-vaccination cycle lengths with those in which a vaccine dose was administered and cycles following vaccination*". "*Cycles in which the single dose of J&J was administered were, on average, 1.26 days longer (95% CI: 0.45, 2.07) than pre-vaccination cycles. […] The conditional logistic regression model of the probability of a long cycle suggested that, compared with pre-vaccination cycles, participants were more likely to experience a long cycle during the cycle in which they received the J&J vaccine[OR=2.17, 95% CI: 1.16, 4.04 (Table 2)]. […] For the J&J dose, follicular phase vaccination was associated with a 2.27 (95% CI: 1.04, 3.50) day increase in cycle length. There was no evidence of increased mean cycle length in cycles in which the first vaccine dose (0.21 days, 95% CI: −0.14, 0.57) or the J&J vaccine dose (0.39 days, 95% CI: −0.75, 1.53) were administered in the luteal phase*". According to the authors, "*Potential mechanisms underlying the change in menstrual cycle length may involve inflammation from the immune response to vaccination. This immune response may impact a) signalling between the hypothalamus, pituitary, and ovaries (HPO), resulting in i) prolongation of follicular recruitment and, as a result, elongation of menstrual cycle length,[…] or ii) suppression of the growth of the endometrial lining,[…] and b) endometrial stability in the luteal phase, causing a reduction in cycle length*". Additional ad-hoc analysis on a menstrual disorder or post-menopausal haemorrhage following vaccination was conducted by the Company based on PRAC request in July 2021 including clinical data and published literature. Based on the literature review, "*there [was] insufficient information to warrant a change to the current RSI or risk minimization and mitigation measures regarding the occurrence of menstrual disorders or post-menopausal haemorrhage following administration of COVID-19 Vaccine Janssen.*" Based on the information available in the Signal Tracking System (STS), "*On 23 February 2022 a signal was identified for Menstrual cycle and uterine bleeding disorders and Postmenopausal haemorrhage with the use of COVID-19 VACCINE AD26.COV2.S based on an aggregate review of post marketing data reported in the Company database and the Food and Drug Administration Vaccine Adverse Event Reporting System database.*" The rationale for creating the signal was "*[…] the impact of the events on patient quality of life and the fact that is a safety topic with regulatory interest.*" However, based on the review of data from the Global Safety database and the FDA Vaccine Adverse Event Reporting System (VAERS), Menstrual cycle and uterine bleeding disorders and Postmenopausal haemorrhage safety signal was not validated and was closed on 25 February 2022. Recently there is an ongoing signal identified in the STS in January 2023 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, that has been validated. Although the study included "*a large sample size (120,815 menstrual cycles from 9,295 participants)*", considering limitations (is based on self-reported data, no laboratory data regarding hormone level measurements, selection biases) of the study, no safety signal was identified at this time.

Rapporteur assessment comment:

This study was conducted by a survey (Apple woman health´s study) in US among female non pregnant subjects not using hormonal contraceptives who actively tracked their menstrual cycles. The noted changeability in length of menstrual cycle was within the natural variability in the study population. No new safety concern was detected.

Nguyen S, Bastien E, Chretien B, et al. Transverse Myelitis Following SARS-CoV-2 Vaccination: A Pharmacoepidemiological Study in the World Health Organization's database. *Ann Neurol.* 2022.
Transverse myelitis (TM) has recently been associated by health authorities with Ad26.COV2.S (Janssen/Johnson & Johnson), 1 of the 5 US FDA or European Medicines Agency (EMA) labeled SARS-CoV-2 vaccines. It is unknown whether a similar association exists for the other FDA or EMA labeled SARS-CoV-2 vaccines (BNT162b2 [Pfizer/BioNTech], mRNA-1273 [Moderna], ChAdOx1nCov-19 [Oxford-AstraZeneca], and NVX-CoV2373 [Novavax]). This study aimed to evaluate the association between SARS-CoV-2 vaccine class and TM.
Methods: This observational, cross-sectional, pharmacovigilance cohort study examined individual case safety reports

from VigiBase, the World Health Organization's pharmacovigilance database. We first conducted a disproportionality analysis with the Information Component (IC) using the reports of TM that occurred within 28 days following exposure to FDA or EMA labeled SARS-CoV-2 vaccines, from 01 December 2020 (first adverse event related to a SARS-CoV-2 vaccine) to 27 March 2022. Secondly, we analysed the clinical features of SARS-CoV-2 vaccine-associated TM cases reported in VigiBase.

Results: TM was significantly associated both with the mRNA-based (n=364; IC 025 =0.62) and vector-based (n=136; IC 025 =0.52) SARS-CoV-2 vaccines that are authorised by the FDA or the EMA.
Conclusions: Findings from this observational, cross-sectional pharmacovigilance study showed that mRNA-based and vector-based FDA/EMA labeled SARS-CoV-2 vaccines may be associated with TM. However, because TM remains a rare event, with a previously reported rate of 0.28 cases per 1 million vaccine doses, the risk-benefit ratio in favour of vaccination against SARS-CoV-2 virus remains unchallenged. Rather, this study suggests that clinicians should consider the diagnosis of TM in patients presenting with early signs of spinal cord dysfunction after SARS-CoV-2 vaccination.
***MAH Comments*:** "*[D]isproportionality analysis yielded significant associations between TM and both mRNA-based and vector-based SARS-CoV-2 vaccines (Table 1), with positive IC025 values of 0.62 and 0.52, respectively. Separately, the IC025 value was 0.69 for BNT162b2 (Pfizer/BioNTech), 0.16 for mRNA1273 (Moderna), 0.21 for ChAdOx1nCov-19 (Oxford–AstraZeneca) and 1.09 for Ad26.COV2.S (Janssen/Johnson & Johnson). […] For the 500 included TM cases, 280 (56%) were after vaccination with BNT162b2 (Pfizer/BioNTech), 84 (17%) after mRNA-1273 (Moderna), 95 (19%) after ChAdOx1nCov-19 (Oxford–AstraZeneca), and 41 (8%) after Ad26.COV2.S (Janssen/Johnson & Johnson) (Table 2).*" TM is currently not listed in the CCDS v13 but is labeled in the EU SmPC. It has been and continues to be an AESI in the EU RMP version 4.2, so the topic is being reviewed, including WHO VigiBase data. This topic was presented in Section 16.3.6.4.7., Transverse Myelitis, in the PBRER covering the period 25 August 2021 through 24 February 2022. According to it, "*Cumulatively, 94 cases (65 medically confirmed and 29 medically unconfirmed) reporting transverse myelitis were identified. […] Based on the review of the literature (ie, Section 11), ongoing/completed clinical studies (ie, Sections 7, 8, and 9), relevant cases retrieved from the Company global safety database in the period and cumulatively, and an O/E analysis, no new critical safety information was identified during the reporting period for transverse myelitis. The Company will continue to closely monitor cases of transverse myelitis as an AESI.*" Currently in the STS there is an ongoing signal identified on 07 December 2022 for the event of "Transverse myelitis" with the use of COVID-19 vaccine AD26.COV2.S based on internal review following routine signal detection activities, that has been validated. The current publication presents 41 cases after the Janssen vaccine from the WHO safety database, which does not provide enough evidence for determining causality association and does not add additional value to the above-mentioned cumulative assessment. No new safety information has been identified at this time.

Rapporteur assessment comment:
Transverse myelitis has been listed in section 4.4 and 4.8 in the SmPC based on in depth analyses performed in SSRs, and a subsequent variation (II-35). No new safety concern was detected here.

Palassin P, Bres V, Hassan S, et al. Comprehensive Description of Adult-onset Still's Disease After COVID-19 Vaccination. *J Autoimmunity*. 2023;134.
Cases of adult-onset Still's disease (AOSD) have been reported after COVID-19 vaccination. Here we provide a comprehensive description and analysis of all cases of AOSD reported in the literature and in pharmacovigilance databases through April 2022. Disproportionality analyses of pharmacovigilance data were performed in order to further explore the association between vaccination and AOSD. We included 159 patients, 144 from the World Health Organization pharmacovigilance database and 15 from the literature. Detailed clinical characteristics were described for the cases from the literature and from the French pharmacovigilance database (n = 9). The cases of AOSD after COVID-19 vaccination concerned women in 52.2% of cases. The median age was 43.4years. More than 80% of AOSD reports occurred during the first 3 weeks and concerned mostly the BNT162b2 mRNA vaccine. We identified 14.5% of disease flare with a median time-to-onset (TTO) of AOSD flare-up significantly shorter than for the new onset form. More than 90% patients received steroids. Although all cases were considered serious and required hospitalisation, most cases presented a favourable outcome (67.1%) with a good response to corticosteroid therapy with a mean time to recovery of 7.2 days. Disproportionality analyses suggested that AOSD was associated with COVID-19 vaccines as well as other vaccines. AOSD was nearly 5times more frequently reported with COVID-19 vaccines than with all other drugs. Clinicians should be informed about the potential risk of AOSD onset or flare following COVID vaccines and the importance of its early detection to optimize its management.
***MAH Comments*:** No new safety information related to Ad26 platform, Disproportionality analyses were conducted to explore the association between vaccination and AOSD. Overall, the study included 159 patients: 144 from the WHO pharmacovigilance database and 15 from the literature for the period up to April 2022. Based on the study results, "*Disproportionality analyses suggested that AOSD was associated with COVID-19 vaccines as well as other vaccines. AOSD was nearly 5 times more frequently reported with COVID-19 vaccines than with all other drugs.*" Out of 159 described cases, only 7 were reported after Janssen vaccine and 37 after AstraZeneca adenovirus-based vaccine. As stated by the authors, "*AOSD after vaccination occurred mostly after the first dose and generally during the first three weeks following vaccination. Interestingly, our study shows a significantly shorter time to onset for flares than for new onset forms.*" In addition, the authors stated, "*Even if a definite causal link between AOSD and COVID-19 vaccination could not be asserted, our disproportionality analyses suggested that COVID-19 vaccines could increase the risk of AOSD.*" According to the latest PBRER covering the period 24 February 2022 to 24 August 2022, "*Acute aseptic arthritis [including Still's disease] is listed as an AESI in the cRMP, EU RMP, and the US PVP."[….] According to the MHA conclusion and PRAC feedback to the latest PBRER(24February 2022 to 24 August/2022)".* Based on the evaluation of the cases, and review of safety from other sources, the information is consistent with the information known about

acute aseptic arthritis. The Company will continue to closely monitor acute aseptic arthritis as an AESI." The reviewed study doesn't provide any safety concern given the known information about acute septic arthritis. Hence, no safety observation is identified at this time.

Rapporteur assessment comment:

The authors have executed disproportionality analysis in pharmacovigilance data for Still´s disease. In total were 159 cases included of which 7 had received JCovden which is a very limited number of subjects. Acute aseptic arthritis (including Still's disease) is listed as an AESI in the RMP and should be closely monitored by the MAH. No new safety concern is detected in this publication.

Patone M, Mei XW, Handunnetthi L, et al. Risk of Myocarditis After Sequential Doses of COVID-19 Vaccine and SARS-CoV-2 Infection by Age and Sex. *Circulation.* 2022. 146;10 (743-754)

Myocarditis is more common after severe acute respiratory syndrome coronavirus 2 infection than after COVID-19 vaccination, but the risks in younger people and after sequential vaccine doses are less certain.

Methods: A self-controlled case series study of people ages 13 years or older vaccinated for COVID-19 in England between 01 December 2020 and 15 December 2021, evaluated the association between vaccination and myocarditis, stratified by age and sex. The incidence rate ratio and excess number of hospital admissions or deaths from myocarditis per million people were estimated for the 1 to 28 days after sequential doses of adenovirus (ChAdOx1) or mRNA-based (BNT162b2, mRNA-1273) vaccines, or after a positive SARS-CoV-2 test.

Results: In 42,842,345 people receiving at least 1 dose of vaccine, 21,242,629 received 3 doses, and 5,934,153 had SARS-CoV-2 infection before or after vaccination. Myocarditis occurred in 2,861 (0.007%) people, with 617 events 1 to 28 days after vaccination. Risk of myocarditis was increased in the 1 to 28 days after a first dose of ChAdOx1 (incidence rate ratio, 1.33 [95% CI, 1.09 to 1.62]) and a first, second, and booster dose of BNT162b2 (1.52 [95% CI, 1.24 to 1.85]; 1.57 [95% CI, 1.28 to 1.92], and 1.72 [95% CI, 1.33 to 2.22], respectively) but was lower than the risks after a positive SARS-CoV-2 test before or after vaccination (11.14 [95% CI, 8.64 to 14.36] and 5.97 [95% CI, 4.54to 7.87], respectively). The risk of myocarditis was higher 1 to 28 days after a second dose of mRNA-1273 (11.76 [95% CI, 7.25 to 19.08]) and persisted after a booster dose (2.64 [95% CI, 1.25to 5.58]). Associations were stronger in men younger than 40 years for all vaccines. In men younger than 40-years-old, the number of excess myocarditis events per million people was higher after a second dose of mRNA-1273 than after a positive SARS-CoV-2 test (97 [95% CI, 91 to 99] versus 16 [95% CI, 12 to 18]). In women younger than 40 years, the number of excess events per million was similar after a second dose of mRNA-1273 and a positive test (7 [95% CI, 1 to 9] versus 8 [95% CI, 6 to 8]).

Conclusion: Overall, the risk of myocarditis is greater after SARS-CoV-2 infection than after COVID-19 vaccination and remains modest after sequential doses including a booster dose of BNT162b2 mRNA vaccine. However, the risk of myocarditis after vaccination is higher in younger men, particularly after a second dose of the mRNA-1273 vaccine.

***MAH Comments*:** Authors used the UK "National Immunisation Database of COVID-19 vaccination to identify vaccine exposure" and linked it "*at the individual level, to national data for mortality (Office for National Statistics), hospital admissions (Hospital Episode Statistics and Secondary User's service data), and SARS-CoV-2 infection data (Second Generation Surveillance System)*" to calculate "*[i]ncidence rate ratios (IRR), the relative rate of hospital admissions or deaths caused by myocarditis in exposure risk periods relative to baseline periods, and their 95% CIs were estimated by the self-controlled case series model adjusted for calendar time*". Authors reported increased risk of myocarditis for AstraZeneca adenoviral vector COVID-19 vaccine within 1 to 28 days after 1st dose (1.33 [95% CI, 1.09 to 1.62]), however it was lower than the risks after a positive SARS-CoV-2 test before or after vaccination (11.14[95% CI, 8.64 to 14.36] and 5.97 [95% CI, 4.54to 7.87], respectively). In the current Janssen COVID-19 vaccine CCDS myocarditis is not a listed event. On 19 July 2021, the signal was opened for myocarditis and pericarditis, and the signal was validated but not confirmed. As per PBRER covering the period from 25 August 2021 to 24 February 2022, "*On 17 October 2021, the Company received feedback from the US Center for Biologics Evaluation and Research (CBER) related to the Emergency Use Authorization (EUA) Amendment 27205 for use of a booster dose of the Janssen COVID-19 vaccine. Within said amendment, CBER proposed the addition of myocarditis and pericarditis to the US Fact Sheets for both Healthcare Practitioners and Recipients and Caregivers. In response to this request, the Company provided a cumulative review of Clinical Trial as well as Post-marketing data with Ad26.COV2.S. Based on the totality of the data, the Company concluded that the available data was insufficient to establish a causal association between Ad26.COV2.S and myocarditis/pericarditis.*". In the US PVP version 5 (internally approved 24 November 2021), myocarditis and pericarditis is listed as an important potential risk. Considering the study design limitations and the lower bound value of the 95% CI no new safety information is detected at this time. Additional information on cardiac inflammatory disorders is found in Section 14, Late-Breaking Information

Rapporteur assessment comment:

On 14 February 2023 a signal was identified for cardiac inflammatory disease (including myocarditis and pericarditis) with the use Ad26.COV2.S based on a request from the US FDA to perform a review of the topic.

Sturkenboom M., Messina D., Paoletti O., de Burgos-Gonzalez et al. Cohort Monitoring of 29Adverse Events of Special Interest Prior to And After COVID-19 Vaccination in Four Large European Electronic Healthcare Data Sources. *MedRxiv*. 2022.

This study aimed to monitor use of COVID-19 vaccines and incidence rates of pre-specified Adverse Event of Special Interest (AESI) of COVID-19 vaccines prior to and after COVID-19 vaccination. This study was not aimed to test a specific hypothesis.
Design: A retrospective cohort study including subjects from 01 January 2020 to 31 October 2021, or latest availability of data.
Setting: Primary and/or secondary health care data from four European (EU) countries: Italy, the Netherlands, the United Kingdom (UK), and Spain.
Participants: Individuals with complete data for the year preceding enrolment or those born at the start of observation time. The cohort comprised 25,720,158 subjects.
Interventions: First and second dose of Pfizer, AstraZeneca, Moderna, or Janssen COVID-19 vaccine.
Main outcome measures (29 AESI): Acute aseptic arthritis, Acute coronary artery disease, Acute disseminated encephalomyelitis (ADEM), Acute kidney injury, Acute liver injury, Acute respiratory distress syndrome, Anaphylaxis, Anosmia or Ageusia, Arrhythmia, Bells' palsy, Chilblain-like lesions death, Erythema multiforme, Guillain BarreSyndrome (GBS), Generalised convulsion, Haemorrhagic stroke, Heart failure, Ischemic stroke, Meningoencephalitis, Microangiopathy, Multisystem inflammatory syndrome, Myo/pericarditis, Myocarditis, Narcolepsy, Single organ cutaneous vasculitis (SOCV), Stress cardiomyopathy, Thrombocytopenia, Thrombotic thrombocytopenia syndrome (TTS), and Venous thromboembolism (VTE).
Results: 12,117,458 individuals received at least a first dose of COVID-19 vaccine: 54% with Comirnaty (Pfizer), 6% Spikevax (Moderna), 38% Vaxzevria (AstraZeneca) and 2% Janssen COVID-19 vaccine. AESI were very rare <10/100,000 PY in 2020, only thrombotic and cardiac events were uncommon. After adjustment for factors associated with severe COVID, 10 statistically significant associations of pooled incidence rate ratios remained based on dose 1 and 2 combined. These comprised anaphylaxis after AstraZeneca vaccine, TTS after both AstraZeneca and Janssen vaccine, erythema multiforme after Moderna, GBS after Janssen vaccine, SOCV after Janssen vaccine, thrombocytopenia after Janssen and Moderna vaccine and VTE after Moderna and Pfizer vaccines. The pooled rate ratio was more than two-fold increased only for TTS, SOCV, and thrombocytopenia.
Conclusion: We showed associations with several AESI, which remained after adjustment for factors that determined vaccine roll out. Hypotheses testing studies are required to establish causality.
***MAH Comments*:** This preprint article presents a retrospective cohort study, which aimed "*to monitor and estimate the incidence rates of AESI in vaccinated and non-vaccinated persons by data source over the period 01 January 2020 to 31 October 2021 by brand and dose of vaccine and to compare the incidence rates of AESI in the window 28 days after vaccination with dose 1 or dose 2 with the incidence rates of AESI of non-vaccinated people in 2020. Overall, 12,117,458 individuals were monitored who received at least a first dose of COVID-19 vaccine: 54% with Comirnaty (Pfizer), 6% Spikevax (Moderna), 38% Vaxzevria (AstraZeneca), and 2% Janssen COVID-19 vaccine.*" *The authors stated that, "After adjustment for the factors associated with vaccination exposure using a Poisson regression, ten pooled (random effects) associations remained for dose (1 and 2) 28-day risk intervals combined, these included […] GBS after Janssen dose 1 (IRR=5.7, 95%CI: 1.4-23), SOCV after Janssen dose 1 (IRR=4.4, 95%CI 1.1-17.7), thrombocytopenia after Janssen dose 1 (IRR=2.3, 95%CI 1.3-4.1), […] TTS after […] Janssen dose 1 (IR=90,10-infinity)*". Based on the authors conclusion, "*[The study] showed associations with several AESI, which remained after adjustment for factors that determined vaccine roll out. Hypotheses testing studies are required to establish causality.*" GBS, TTS, and immune thrombocytopenia (ITP) are listed adverse drug reactions (ADR) for Janssen vaccine in the CCDS. However, for cutaneous vasculitis there is an ongoing signal in STS. It is labeled in the EU Summary of Product Characteristics (SmPC) but not listed in the Janssen CCDS. According to the Pharmacovigilance Risk Assessment Committee (PRAC) feedback in the latest PBRER covering the period of 24 February 2022 to 24 August 2022, "*On 31 August 2022, both thrombocytopenia and SOVC were identified to have an association with Ad26.COV2.S from the review of the VAC4EU COVID vaccine safety monitoring system. Both events are already listed as adverse reactions following earlier assessments from the European Medicines Agency PRAC as immune thrombocytopenia and cutaneous small vessel vasculitis respectively. After the data lock point, the Company opened a safety signal based on the disproportionate reporting of vasculitis, particularly cutaneous vasculitis. The evaluation of this signal is ongoing and will be presented in the next PBRER.*"

Rapporteur assessment comment:

A retrospective cohort study based on health care data from Italy, Netherlands and the UK, where the frequency of 29 AESIs were executed. GBS, TTS and ITP are already listed as ADRs. No new safety concern was noted.

Class Effect Literature

Beltrami-Moreira M, Bussel JB. A Narrative Review of Anti-SARS-COV-2 Vaccines and Immune Thrombocytopenia: Be Aware, But Reassured. *Clin Adv Hematol. Oncol.* 2022;20(9):572-578.
The COVID-19 pandemic gave rise to rapid development of anti-SARS-COV-2 vaccines using established and new technologies. Immune thrombocytopenia (ITP) is a bleeding disorder that has been associated with COVID-19 vaccine products that are currently in use. We reviewed the available evidence regarding the most commonly used vaccines against SARS-COV-2 in North America and Europe and their association with ITP. We found that population-based studies suggested a small increase in the incidence of ITP in persons receiving the ChAdOx1 nCoV-19 vaccine from Oxford-AstraZeneca, on the order of 6 cases per million doses administered. Severe bleeding was an even rarer event. Both mRNA-based and adenovirus-based vaccines have been associated with exacerbation of preexisting ITP in 6% to 20% of patients. ITP exacerbation is readily treatable with standard approaches when needed. Severe bleeding events

are rare both in the general population and in persons with preexisting ITP, and overall, the benefits of vaccination outweigh the risks. Further identification of persons at the highest risk for complications (including those with ITP, VITT, and myocarditis) and clear communication of both risks and benefits of immunisation will continue to be paramount in the global campaign against COVID-19.
MAH Comments: *This review article commented on the risk of ITP following immunisation with COVID-19 vaccines. Overall, the authors indicate available data suggests a small increase in cases of ITP in subject receiving ChAdOx1 (a vector-based vaccine) compared to mRNA vaccines. However, both mRNA and adenovector vaccines have been associated with an exacerbation of pre-existing ITP. Severe bleeding was very rare. ITP is considered an Important Potential Risk in the cRMP and US PVP, and as an Important Identified Risk (IIR) in the EU RMP (as 'Thrombocytopenia, including ITP'). A warning text also exists in the CCDS and EU Summary of Product Characteristics (SmPC) on the risk of bleeding in patients with a history of ITP. No new safety concern is identified form review of this data.*

Rapporteur assessment comment:

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

Borghi MO, Bombaci M, Bodio C, et al. Anti-phospholipid Antibodies And Coronavirus Disease 2019: Vaccination Does Not Trigger Early Autoantibody Production in Healthcare Workers. *Front. Immunol.* 2022;13: 930074. A molecular mimicry between SARS-COV-2 and human proteins supports the possibility that autoimmunity takes place during COVID-19 contributing to tissue damage. For example, anti-phospholipid antibodies (aPL) have been reported in COVID-19 as a result of such mimicry and thought to contribute to the immunothrombosis characteristic of the disease. Consistently, active immunisation with the virus spike protein may elicit the production of cross-reactive autoantibodies, including aPL. We prospectively looked at the aPL production in HCW vaccinated with RNA- (BNT162b2, n. 100) or adenovirus-based vaccines (ChAdOx1, n. 50). Anti-cardiolipin, anti-beta2 glycoprotein I, anti-phosphatidylserine/prothrombin immunoglobulin G (IgG), IgA, and IgM before and after vaccination were investigated. Anti-platelet factor 4 immunoglobulins were also investigated as autoantibodies associated with COVID-19 vaccination. Additional organ (anti-thyroid) and non-organ (anti-nuclear) autoantibodies and IgG against human proteome were tested as further post-vaccination autoimmunity markers. The antibodies were tested 1 or 3 months after the first injection of ChAdOx1 and BNT162b2, respectively; a 12-month clinical follow-up was also performed. Vaccination occasionally induced low titres of aPL and other autoantibodies but did not affect the titre of pre-existing autoantibodies. No significant reactivities against a microarray of approximately 20,000 human proteins were found in a subgroup of ChAdOx1-vaccinees. Consistently, we did not record any clinical manifestation theoretically associated with an underlying autoimmune disorder. The data obtained after the vaccination (2 doses for the RNA-based and 1 dose for the adenovirus-based vaccines), and the clinical follow-up are not supporting the occurrence of an early autoimmune response in this cohort of healthcare workers.
MAH Comments: *The authors in the article explored the hypothetical production of aPL following COVID-19 vaccination as possible contributors for the onset of thrombosis in COVID-19 vaccine recipients. The authors also measured other autoimmune markers such as PF4, anti-cardiolipin, anti-beta2 glycoprotein I, anti-phosphatidylserine/prothrombin IgG, IgA, and IgM. Overall, the authors did not find evidence supporting the occurrence of an early autoimmune response. TTS is considered an IIRfollowing vaccination with Ad26.COV2.S. Cerebrovascular events are listed as an AESI in the cRMP, EURMP, and USPVP. The mechanism behind TTS is not yet fully understood. No safety concern is identified based on the results from this study.*

Rapporteur assessment comment:

The authors have looked prospectively at the production of cross-reactive autoantibody aPL following Covid-19 vaccination. No association with an early autoimmune response was noted in this study.

Garabet L, Eriksson A, Tjonnfjord E, et al. No Increase in Thrombin Generation or D-Dimer Levels After Anti-SARS-COV-2 Vaccines Including in Those With Anti-Platelet Factor 4Antibodies. *Hemasphere.* 2022;6(Supplement 3):2956-2957.
Anti-SARS-COV-2 adenoviral-vectored-DNA vaccines have been linked to a rare but serious thrombotic post-vaccine complication called the VITT. VITT has raised concerns regarding the possibilities of increased thrombotic risk and thrombocytopenia after anti-COVID-19 vaccines.
Aim: To investigate whether anti-SARS-COV-2 vaccines can cause thrombocytopenia, coagulation activation and increased thrombin generation leading to a hypercoagulable state.
Methods: In this study, 567 healthcare personnel were included from 2 hospitals in Norway after obtaining informed consent. Of these, 521 were recruited 11 to 57 days post-vaccination with the first dose of ChAdOx1-S (Vaxzevria, AstraZeneca, UK) vaccine, and 46 were recruited prospectively prior vaccination with an mRNA vaccine, either elasomeran (Spikevax, Moderna, n=38) or tozinameran (Comirnaty, Pfizer-BioNTech, n=8). In the latter group, samples were acquired before and 1 to 2 weeks after vaccination. In addition to pre-vaccination samples, 56 unvaccinated healthy blood donors were recruited as controls (total n=102). Thrombin generation and D-dimer were analysed.
Results: None of the participants developed thrombosis/VITT;12% reported cutaneous bleeding after vaccination; however, none had thrombocytopenia with platelet count <100.109/L. There were no significant differences in D-dimer or the parameters of thrombin generation between the 2 vaccine groups and the controls. Anti-PF4/polyanion antibodies (optical density >=0.4) were found in 11 of 513 individuals vaccinated with ChAdOx1-S vaccine (2.1%). None of the controls had anti-PF4/polyanion antibodies. Thrombin generation and D-dimer were not found to be higher in the ChAdOx1-S vaccinated individuals with anti-PF4 antibodies than in those without anti- PF4/polyanion antibodies.

No differences in thrombin generation between the ChAdOx1-S group and the mRNA group. The median D-dimer level was slightly higher in the ChAdOx1-S group than the mRNA group, but both were within the normal range. Thrombin generation and D-dimer showed no changes after mRNA vaccination compared with baseline.
Conclusion: Anti-COVID-19 vaccines, both ChAdOx1-S and mRNA vaccines, did not lead to an increase in thrombin generation or D-dimer compared with controls, not even in the ChAdOx1-S vaccinated individuals with anti-PF4/polyanion antibodies. No differences were found between ChAdOx1-S and mRNA vaccines, and no increase in thrombin generation or D-dimer was found after mRNA vaccines compared with baseline levels. Our results are reassuring in the sense that no subclinical activation in the coagulation system was observed with these vaccines.
MAH Comments: *The authors in the article explored the increase in thrombin or D-dimer levels in healthy HCWs vaccinated with either mRNA or adenovector (ChAdOx1) COVID-19 vaccine compared to unvaccinated controls. No increase in thrombin generation or D-dimer was observed compared with controls for either adenovector nor mRNA vaccines. The results were reassuring, as no subclinical activation in the coagulation system was observed. Venous Thrombotic events as well as Thrombocytopenia (including ITP) remain IIRs for Ad26.COV2.S. No safety concern is identified based on the results from this study.*

Rapporteur assessment comment:

A Norwegian study including 567 healthcare personnel with the aim to investigate whether Covid-19 vaccines could cause thrombocytopenia, coagulation activation and increased thrombin generation. The first administered dose was the adenovirus-based AZ-vaccine. None of the subjects received JCovden.

Venous thromboembolism, thrombosis in combination with thrombocytopenia and immune thrombocytopenia are already included in the product information. No new safety concern was noted in this study.

Magdy R, Khedr D, Yacoub O, Attia A, Abdelrahman MA, Mekkawy D. Epidemiological Aspects of Headache After Different Types of COVID-19 Vaccines: An Online Survey. *Headache*. 2022;62(8):1046-1052.
COVID-19 vaccine-related side effects are a key concern with the emergence of various types of vaccines in the market. We aimed to assess the frequency and characteristics of headache following different types of COVID-19 vaccines.
Methods: Fully vaccinated people were recruited by a convenience sample through an online survey from 01 September 2021 to 01 December 2021. Detailed analysis of headache following vaccination was investigated. Participants with a history of pre-existing headaches were telephone interviewed by a neurologist to ascertain the type of headache.
Results: A total of 1,372 participants participated (mean age 32.9 +/- 11.1). The highest frequency of headache was reported with the adenoviral vector type (302/563, 53.6%), followed by mRNA vaccines (129/269, 48%) and then the inactivated type (188/540, 34.8%). Recipients of the adenoviral vector type had a significantly longer latency between vaccination and the headache onset (median 8 hours [5:12]) than recipients of the inactivated type (median 4 hours [2:8], $p < 0.001$). Headache intensity was significantly higher with the adenoviral vector type (median 6 [5:8]) than with the inactivated type (median 5 [4:7], $p < 0.001$). Adenoviral vector vaccines would increase the likelihood of headache by 2.38 times more than inactivated vaccines (odds ratio [OR] 2.38, 95% confidence interval [CI] 1.83 to 3.04, $p < 0.001$). Female sex and thyroid disease were significantly associated with headache related to COVID-19 vaccines (OR 1.52, 95% CI 1.16 to 1.99, OR 3.97, 95% CI 1.55to 10.2, respectively).
Conclusion: Recipients of the COVID-19 vaccine should be counseled that they may experience headaches, especially after the adenoviral vector type. However, the intensity of such headache is mild to moderate and can resolve within a few days. Based on the current study design and the potential recall bias, these results may not be generalisable and should be preliminary.
MAH Comments: *This comparative observational study showed a higher frequency of headache compared to mRNA vaccines and higher severity compared to inactivated vaccines. Overall, however, these episodes were mild and transient in nature. Headache is a very common ADR following Ad26.COV2.S, generally as a result of vaccine reactogenicity. The findings from this study are consistent with the known reactogenicity profile of Ad26.COV2.S from clinical trial experience. No safety concern is identified.*

Rapporteur assessment comment:

Headache is already included as an ADR in the SmPC section 4.8 with a frequency "very common". No new safety concern was detected here.

Stefanou MI, Palaiodimou L, Aguiar de Sousa D, et al. Acute Arterial Ischemic Stroke Following COVID-19 Vaccination: A Systematic Review And Meta-analysis. *Neurol.* 2022; 99(14):e1465-e1474.
Acute arterial-ischemic-stroke (AIS) has been reported as a rare AE following COVID-19 vaccination with mRNA or viral vector vaccines. However, data are sparse regarding the risk of post-vaccination AIS and its potential association with TTS.
Methods: A systematic review and meta-analysis of randomised-controlled clinical trials (RCTs), pharmacovigilance registries, registry-based studies, observational cohorts and case-series was performed with the aim to calculate: (1) the pooled proportion of patients presenting with AIS following COVID-19 vaccination; (2) the prevalence of AIS after

mRNA and vector-based vaccination; (3) the proportion of TTS among post-vaccination AIS-cases. Patient characteristics were assessed as secondary outcomes.
Results: Two RCTs, 3 cohort, and 11 registry-based studies comprising 17,481 AIS-cases among 782,989,363 COVID-19 vaccinations were included in the meta-analysis. The pooled proportion of AIS following exposure to any COVID-19 vaccine type was 4.7 cases per 100,000 vaccinations (95%CI:2.2 to 8.1; *I2*=99.9%). The pooled proportion of AIS following mRNA-vaccination (9.2 cases per 100,000 vaccinations; 95%CI: 2.5-19.3; *I2*=99.9%) did not differ compared to adenovirus-based-vaccination (2.9 cases per 100,000 vaccinations; 95%CI: 0.3 to 7.8; *I2*=99.9%). No differences regarding demographics were disclosed between patients with AIS following mRNA- or vector-based vaccination. The pooled proportion of TTS among post-vaccination AIS-cases was 3.1% (95%CI: 0.7 to 7.2%; *I2*=78.8%).
Conclusions: The pooled proportion of AIS following COVID-19 vaccination is comparable to the prevalence of AIS in the general population and much lower than the AIS prevalence among SARS-COV-2-infected patients. TTS is very uncommonly reported in patients with AIS following COVID-19 vaccination.
MAH Comments: *The article presents a systematic review and meta-analysis of cases of AIS following COVID-19 vaccination. In particular, the authors explored the differences in the frequency of AIS between mRNA and vector-based COVID-19 vaccines. Overall, the pooled proportion of AIS did not differ between vaccine types. TTS was rarely reported among AIS cases. TTS is considered an Important Identified Risk following vaccination with Ad26.COV2.S. Cerebrovascular events are listed as an AESI in the cRMP, EURMP, and USPVP. No safety concern is identified based on the results from this study.*

Rapporteur assessment comment:

The authors who performed this review and meta-analysis study concluded that the pooled proportion of acute arterial-ischemic-stroke (AIS) following COVID-19 vaccination is comparable to the prevalence of AIS in the general population and that TTS is very uncommonly reported in patients with AIS following COVID-19 vaccination.

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

Wang JJ, Armour B, Chataway T, et al. Vaccine-induced Immune Thrombotic Thrombocytopenia (VITT) is Mediated by a Stereotyped Clonotypic Antibody. *MedRxiv.* 2022.
Vaccine-induced immune thrombotic thrombocytopenia (VITT) is a rare thromboembolic complication of adenoviral-vectored severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) vaccines, mediated by antibodies directed against platelet factor 4 (PF4). Given their causal role in VITT, identification of the molecular composition of anti-PF4 antibodies is crucial for developing better diagnostics and treatments. Here, we utilised a novel proteomic workflow to analyse the immunoglobulin variable (IgV) region composition of anti-PF4 antibodies at the level of the secreted proteome. Serum anti-PF4 IgG antibodies from 5patients with VITT triggered by ChAdOx1 nCoV-19 vaccination were affinity purified by PF4-coupled magnetic beads and sequenced by mass spectrometry. We revealed a single IgG heavy (H)-chain species paired with a single lambda light (L)-chain species in all 5 unrelated patients. Remarkably, all L-chains were encoded by the identical IGLV3-21*02 gene subfamily with identical L-chain third complementarity determining region (LCDR3) lengths. Moreover, striking stereotypic features were also identified in heavy-chains anti-PF4 antibodies characterised by identical HCDR3 length and homologous sequences. In summary, we unraveled the molecular signature of highly stereotyped clonotypic anti-PF4 antibodies, indicating shared pathways of antibody production in VITT patients. These discoveries are critical to understand the molecular basis of this serious condition and develop novel therapies aimed at removing pathogenic clones.

MAH Comments: *This proteomic analysis showed a highly stereotyped clonotypic anti-PF4 antibodies among 5 unrelated patients who developed VITT following vaccination with ChAdOx1, indicating shared pathways of antibody production in VITT patients. The mechanism for TTS (VITT) following vaccination with AD26.COV2.S remains unknown. No safety concern was identified from this study. The Company will continue to study the possible mechanistic pathways for TTS following vaccination.*

Rapporteur assessment comment:

The authors have set up a proteomic workflow to analyse the variable region (IgV) of anti-PF4 antibodies. No new safety concern was detected here.

Xie J, Prats-Uribe A, Gordillo-Maranon M, Strauss VY, Gill D, Prieto-Alhambra D. Genetic Risk and Incident Venous Thromboembolism in Middle-aged and Older Adults Following COVID-19 Vaccination. *J Thromb Haemost.* 2022;20(12):2887-2895.
COVID-19 vaccination has been associated with increased venous thromboembolism (VTE) risk. However, it is unknown whether genetic predisposition to VTE is associated with an increased risk of thrombosis following vaccination.
Methods: Using data from the UK Biobank, which contains in-depth genotyping and linked vaccination and health outcomes information, we generated a polygenic risk score (PRS) using 299 genetic variants. We prospectively assessed associations between PRS and incident VTE immediately after first- and the second-dose vaccination and

among historical unvaccinated cohorts during the pre- and early pandemic. We estimated hazard ratios (HR) for PRS-VTE associations using Cox models.
Results: Of 359,310 individuals receiving 1 dose of a COVID-19 vaccine, 160,327 (44.6%) were males, and the mean age at the vaccination date was 69.05 (standard deviation [SD] 8.04) years. After 28- and 90-days follow-up, 88 and 299 individuals developed VTE, respectively, equivalent to an incidence rate of 0.88 (95%[CI] 0.70-1.08) and 0.92 (0.82-1.04) per 100,000 person-days. The PRS was significantly associated with a higher risk of VTE (HR per 1 SD increase in PRS, 1.41 (1.15to 1.73) in 28 days and 1.36 (1.22 to 1.52) in 90 days). Similar associations were found in the historical unvaccinated cohorts.
Conclusions: The strength of genetic susceptibility with post-COVID-19-vaccination VTE is similar to that seen in historical data. Additionally, the observed PRS-VTE associations were equivalent for adenovirus- and mRNA-based vaccines. These findings suggest that, at the population level, the VTE that occurred after the COVID-19 vaccination has a similar genetic aetiology to the conventional VTE.
MAH Comments: *The authors conducted a prospective cohort study to assess a self-generated PRS and the risk of VTE. The PRS was significantly associated with a higher risk of VTE (HR per 1 SD increase in PRS, 1.41 [1.15 to 1.73] in 28 days and 1.36 [1.22 to 1.52] in 90 days). In addition, the observed PRSVTE associations were equivalent for adenovirus- and mRNA-based vaccines. VTE is listed as an IIR for Ad26.COV2.S in the RMP. The findings from this study suggest the risk of VTE following vaccination may be linked to genetic predispositions.*

Rapporteur assessment comment: The authors have used data from UK Biobank to investigate genetic predisposition for VTE in association with covid-19 vaccination. No new safety concern was noted here.

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

efficacious against severe/critical COVID-19, including hospitalisations and deaths related to COVID-19, including against some variants. While the analysis of Delta cases from clinical trials remains inconclusive, multiple sources of evidence confirm vaccine effectiveness against observed COVID-19 and COVID-19-related hospitalisation related to the Delta and Omicron VOC in a real-world setting. Overall, there is no safety concern related to lack of efficacy.

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

1.3.7. Late-breaking information

Update to US Emergency Use Authorisation Fact Sheet
On 13 March 2023, the US Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers) was updated to include a new Warning and Precautions statement for myocarditis and pericarditis. Of note, the 13 March 2023 updated Healthcare Providers Fact Sheets also included the final agreement to update the adverse reactions section for 'facial paralysis (including Bell's palsy)' with the updated Recipient and Caregivers Fact Sheet including 'weakness or paralysis of the muscles of the face'.

Myocarditis/Pericarditis
On 31 March 2023, EU/EMA was notified of an Internally-identified Significant Safety Issue (IISS) of myocarditis and pericarditis classified as an Emerging Safety Issue (ESI).
Whilst the mechanism of action is not clearly established, the potential impact to public health of this disease and consistency of data justifies adding it as a safety concern for the vaccine, as an IIR in the cRMP.
Request: On 08 March 2023, the US FDA communicated that the US Fact Sheets should be amended to reflect an elevated risk of myocarditis and pericarditis.

MAH Conclusion: Based on the totality of data, particularly the most recent age and sex stratified RWE RCA outcome, myocarditis and pericarditis are considered ADRs (both assigned a reporting frequency of very rare) and an important identified risk (IIR) associated with the use of Ad26.COV2.S. Key factors supporting this conclusion include:
• A potential mechanism of action hypothesising hypersensitivity reaction to circulating Spike protein compared to healthy vaccinated individuals following mRNA vaccines, may be applicable to Ad26.COV2.S.
• Although no disproportionality was observed in VAERS or WHO VigiBase at either High Level Term (HLT) or PT levels, disproportionality was observed myocarditis and pericarditis in the Company global safety database and EudraVigilance.
• For the post-marketing spontaneous cases, most of the cases were assessed as Brighton Collaboration (BC) Level 4 and Level 5, indicating cases providing insufficient information to meet Level 1, 2, or 3, or there were clear alternative explanation to explain the event onset. However, several BC Level 1 to 3 cases were reported in close temporal association to the vaccine for which causality could not be excluded, and in particular, several BC level 2 cases that were reported among males under 40 years of age.
• The restricted O/E analysis for myocarditis indicated statistically significant differences in observed counts following exposure with Ad26.COV2.S for most, though not all, females and males in the 18 to 29, 30 to 39, 40 to 49, and 50 to 64 age groups in the US and EU, across the 3 risk windows. This was found more consistently in the male groups. The restricted O/E analysis for pericarditis indicated a statistically significant difference in observed counts following exposure with Ad26.COV2.S for only the US female 30 to 39 age group in the 1 to 7 day risk window.
• The RWE RCA indicates a high level of certainty of an increased risk of myocarditis and pericarditis for

males aged 18 to 39 years post vaccination with Ad26.COV2.S. The increased risk was observed consistently across all 3 US claims databases and between different methods (i.e., a Self-Controlled Case Series and comparative cohort) as well as different risk windows.
The global spontaneous reporting rate of myocarditis and pericarditis for primary dose vaccination (cases of BC levels 1 to 4) was estimated at 4.32 and 4.15, respectively, per million doses administered; the assigned frequency category is: very rare. The global spontaneous reporting rate of myocarditis and pericarditis for booster dose vaccination (cases of BC levels 1 to 4) was estimated at 4.47 and 2.55, respectively, per million doses administered; the assigned frequency category is: very rare.

Rapporteur assessment comment:

In a letter from the MAH to the EMA dated 31 March 2023, the MAH conclude that the available safety data, the supports a reasonable possibility of a causal association between Ad26.COV2.S and myocarditis and pericarditis. In the cover letter to this PBRER, the MAH confirm that in line with the request to submit a Type II variation to address myo-/pericarditis as an important identified risk for JCOVDEN by 17 April 2023, the MAH has submitted a variation, including updated EUPI and EU-RMP version 6.2 on 14 April 2023 (EMEA/H/C/005737/II/072/G). This variation was discussed by the PRAC in May 2023, and CHMP adopted an opinion in line with the PRAC's review which concluded on the need for an update the product information (sections 4.4 and 4.8, and the PIL accordingly).

It should also be mentioned that after the DLP of this PSUR the FDA announced the following decision on the revocation of the Emergency Use Authorisation (EUA) for Janssen COVID-19 vaccine as of June 1st:

"On Thursday, the FDA revoked the emergency use authorization (EUA) of the Janssen COVID-19 Vaccine. On May 22, Janssen Biotech Inc. requested the voluntary withdrawal of the EUA for this vaccine. Janssen Biotech, Inc. informed the FDA that the last lots of the vaccine purchased by the U.S. government have expired, there is no demand for new lots of the vaccine in the U.S., and they do not intend to update the strain composition of this vaccine to address emerging variants."

2. Signal and risk evaluation

2.1. Summary of safety concerns

At the beginning of the Reporting Period

The summary of safety concerns at the beginning of the reporting period to be included in the Ad26.COV2.S PBRER are based on cRMP (version 5.0, dated 24 May 2022) and are summarised in the table below:

Table 42: Important Identified Risks, Important Potential Risks and Missing Information at the Beginning of the Reporting Period

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

Key: ITP=Immune Thrombocytopenia

a: Venous thromboembolism is an important identified risk in European Union Risk Management Plan version 4.2.

b: ITP is characterised in the European Union Risk Management Plan version 4.2 as Important Identified Risk "Thrombocytopenia, including ITP".

At the End of the Reporting Period

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

• The cRMP version 5.0 was updated to version 6.0 on 25 October 2022 with the reclassification of important potential risk of venous thromboembolism to an important identified risk.

The updated summary of safety concerns is presented below:

Table 43: Important Identified Risks, Important Potential Risks and Missing Information at the End of the Reporting Period

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

Key: ITP=Immune thrombocytopenia

a: ITP is characterised in the European Union Risk Management Plan version 5.3 as Important Identified Risk "Thrombocytopenia, including ITP".

It should be noted that both the cRMP and the EU RMP are in the process of being updated with the inclusion of myocarditis and pericarditis as an IIR.

Rapporteur assessment comment:

During the reporting interval, venous thromboembolism has been reclassified from important potential risk to important identified risk. There is an ongoing process of the MAH to include myocarditis and pericarditis as an important identified risk in the cRMP.

2.2. Signal evaluation

2.2.1. Ongoing or closed signals

Tabular overview of signals: new, ongoing or closed during the reporting interval 23 Aug 2022 to 24 Feb 2023.

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
Cutaneous Vasculitis	01/Sep/2022	NEW SIGNAL; CLOSED/ SAFETY ISSUE NOT-CONFIRMED	24/Feb/2023	Internal Signal Detection - World Health Organization VigiBase;	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 01SEP2022 a signal was identified for the event Cutaneous Vasculitis with the use of COVID-19 Vaccine Ad26.COV2.S based on a statistical signal of disproportionate reporting identified within the World Health Organization VigiBase.; This signal was reassessed due to the possible overlap / mechanism for large vessel vasculitis (greater medical significance). This signal was reassessed due to the question of can patients be re-vaccinated with an Ad26 vaccine after an episode of cutaneous vasculitis? This signal was reassessed due to it being labeled in Summary of Product Characteristics as 'cutaneous small vessel	The evaluation method included a cumulative case series review of available data in the Global Safety Database through 24AUG2022 (n=176 cases; Post marketing cases) reporting the Preferred Terms from the Medical Dictionary for Regulatory Activities (MedDRA) Standardised MedDRA Query: Vasculitis. The cases were individually assessed to classify them according to their type (Small, medium and large vessel vasculitis). For this analysis, only cases concerning small vessel vasculitis were included. Data mining analysis of the Food and Drug Administration Vaccine Adverse Event Reporting System, EudraVigilance, and	Close monitoring as Adverse event of special interest continued.
					vasculitis' and because of four well-documented literature cases of leukocytoclastic vasculitis.	World Health Organization VigiBase was performed. Analysis of relevant clinical trial data, analysis of relevant data from observational databases, calculation of reporting rates of the events, a drug-class labeling comparison, and a review of relevant scientific literature was performed.	
Cerebral haemorrhage	12/Dec/2022	NEW SIGNAL; ONGOING/ EVALUATION	---	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.		
Transverse myelitis	07/Dec/2022	NEW SIGNAL; CLOSED/ SAFETY ISSUE CONFIRMED	27/Jan/2023	Internal Signal Detection - Company Database - Aggregate, Internal Signal Detection - Company Database - Single case assessment , Internal Signal Detection - EudraVigil ance, Internal Signal Detection - Food and Drug Administra tion Vaccine Adverse Event Reporting System, Internal Signal Detection - World Health Organizati on VigiBase, Literature, Observatio nal (epidemiol ogy) database	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 07DEC2022 a signal was identified for the event of Transverse myelitis with the use of COVID-19 VACCINE AD26.COV2.S based on internal review following routine signal detection activities. This signal was reassessed due to the fact that is a safety topic with regulatory interest. This signal was reassessed due to biological plausibility, due to the significant case volume, due to the appearance of 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.	The evaluation method included a cumulative case series review of available data in the Global Safety Database through 24AUG2022 (n=112 cases; 112 primary dose cases and 2 booster dose cases) reporting the following Medical Dictionary for Regulatory Activities Preferred Terms: Acute flaccid myelitis, Myelitis, Myelitis transverse, Noninfectious myelitis, Autoimmune demyelinating disease, Immunemediated neurological disorder, Neuromyelitis optica pseudo relapse, Neuromyelitis optica spectrum disorder, Noninfective encephalomyelitis, and Demyelination. Data mining analysis of the Food and Drug Administration Adverse Event Reporting System, EudraVigilance, and World Health Organization VigiBase was performed. Analysis of relevant clinical trial data, analysis of relevant data from observational databases (Real World Evidence Rapid Cycle Analytics), drug-class labeling comparison, and a review of relevant scientific literature was performed.	Change to Reference Safety Information/ Labeling: Company Core Data Sheet update, Change to local labeling/pack age insert, Investigator's Brochure update, and Update to patient information.; Routine Pharmacovig ilance (PV) Activities. Event was previously closely monitored as an Adverse Event of Special Interest (AESI). Following the confirmation of this signal, the event will be removed from the AESI list and continued to be followed-up through regular PV activities.

Heavy menstrual bleeding	17/Jan/2023	NEW SIGNAL; ONGOING/ EVALUATION	---	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 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.	---	---
Myocarditis and Pericarditis	14/Feb/2023	NEW SIGNAL; ONGOING/ EVALUATION	---	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 (incl. 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.	---	---
Postural Orthostatic Tachycardia Syndrome	22/Feb/2023	NEW SIGNAL; ONGOING/ EVALUATION	---	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	---	---

					Spoke component of the vaccine and ACE2 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.		

Key: Ad26.COV2.S=Adenovirus Type 26.Coronavirus 2.Spike; AESI=Adverse Event of Special Interest; COVID-19=Coronavirus Disease-2019; Inc.=Including; MedDRA=Medical Dictionary for Regulatory Activities; n=Number of Cases; PBRER/PSUR=Periodic Benefit Risk Evaluation Report/Periodic Safety Update Report; POTS=Postural Orthostatic Tachycardia Syndrome; PRAC=Pharmacovigilance Risk Assessment Committee; PV=Pharmacovigilance

Rapporteur assessment comment:

During the reporting interval the following signals were ongoing or closed: cutaneous vasculitis (closed, safety issue not confirmed but closely monitoring will continue), cerebral haemorrhage (ongoing), transverse myelitis (closed, safety issue confirmed, and SmPC section 4.4 and 4.8 has been updated), heavy menstrual bleeding (ongoing), myocarditis/pericarditis (ongoing) and postural orthostatic tachycardia syndrome (ongoing).

All ongoing signals except myo/pericarditis, which has been assessed in variation II-72G, should be presented in the next PSUR.

2.2.2. Regulatory Authority Requested Topic

Myocardial Infarction

Request: On 18 May 2022, the Company received the following request from the Canadian Marketed Health Products Directorate following review of the first Bi-Monthly Safety Report for the Janssen COVID-19 vaccine (Ad26.COV2.S [recombinant]) covering the period of 01 November 2021 to 15January 2022:

"Provide a detailed Brighton Collaboration level criteria and causality assessment for myocardial infarction cases cumulatively up to the data lock point ofthe next PBRER. This cumulative review should include analyses of any additional cases, and an updated observed-to-expected analyses (stratified by age and gender, where possible). Include a summary of data from ongoing safety studies and relevant published literature in your response. Provide a copy of the assessment of myocardial infraction and other safety signals identified by other regulators in the next PBRER."

MAH Conclusion: Based on review of the totality of available data, there is insufficient evidence to support a causal association between myocardial infarction (MI) and the Ad26.COV2.S vaccine. Key factors supporting this conclusion include lack of established biological plausibility, no increased risk observed from review of a large clinical trial datasets, and insufficient evidence from aggregate post-marketing spontaneous reports as well as the biomedical literature. The Company will continue to monitor events of MI via routine PV activities.

Rapporteur assessment comment:

In the last PSUR (EMEA/H/C/PSUSA/00010916/202208), an in-depth analysis on myocardial infarction in the first 2 weeks following vaccination was performed. No causal association was established, and the signal was closed which is endorsed.

IgA Nephropathy

Request: In its assessment report on the Annual Renewal of the Conditional Marketing Authorisation for JCOVDEN covering the reporting period of 01 August 2021 to 31 July 2022; Addendum to Clinical Overview (ACO), (procedure number: EMEA/H/C/005737/R/0063), the Committee for Medicinal Products for Human use (CHMP) requested more details on the signal of Immunoglobulin A Nephropathy (IgA), that had been closed at the time of the ACO.

MAH Conclusion: In the ACO with the reporting period covering 01 August 2021 to 31 July 2022, IgA nephropathy was succinctly presented as a signal closed during the reporting period. Following the submission of the ACO in the context of the renewal procedure, and in line with the request of CHMP, a cumulative ad-hoc analysis on glomerulonephritis and nephrotic syndrome, including IgA nephropathy has been presented in the 3rd PBRER with reporting dates of25February 2022 to 24August 2022.
The cumulative ad-hoc analysis included all the 3 cases with IgA nephropathy received cumulatively. Therefore, presentation of the ad-hoc analysis in the 3rd PBRER, submitted after the ACO, addressed the above-mentioned request. The analysis concluded that based on the totality of the cumulative post-marketing and clinical trial data, and the comprehensive literature review, there is insufficient information to suggest an association between Ad26.COV2.S and the occurrence of glomerulonephritis and nephrotic syndrome. In the second updated PRAC Rapporteur AR (PRAC AR 2023) for the 3rd PBRER (procedure number: EMEA/H/C/PSUA/0010916/202208), circulated on 04 April 2023, PRAC endorsed the MAH's conclusion on the analysis as follows:
"In the previous PSUR there was a request to present a cumulative review of Glomerulonephritis and Nephrotic Syndrome as supplementary information. The MAH responded within the last PSUR presenting a cumulative review on all cases of GN and NS. Data have been also submitted with this PSUR. Based on these data, the PRAC concluded that there was no need for additional actions."
Since the DLP of the 3rd PBRER (24August 2022), and during the reporting period of the current PBRER (25August 2022 to 24February 2023), one further case with IgA nephropathy has been received in the Company global safety database. Assessment of this case, sourced from literature (Petrou) did not change previous conclusions on this topic, as it involved a small case series with several patients, including 1 patient who experienced nephrotic syndrome as a result of IgA nephropathy relapse without any further information on the patient's clinical course, medical history, concomitant medications, time to onset (TTO), and outcome of the events. The Company will continue to monitor glomerulonephritis and nephrotic syndrome, including IgA nephropathy via routine pharmacovigilance activities.

Rapporteur assessment comment:

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

Severe Cutaneous Adverse Reactions

Request: The second updated PRAC Rapporteur AR for the 3rd Ad26.COV2.S PBRER, (25February 2022 to 24 August 2022), circulated on 04April 2023, (procedure number: EMEA/H/C/PSUSA/000106/202208), (PRAC AR 2023) requested the Company address the following in the current PBRER:
"Severe cutaneous adverse reactions have been evaluated in previous procedures, but there are some time periods which have not been reviewed. For the next PSUR, the period 25 February 2022 to 24 February 2023 should be specifically analysed, inclusive high-level analysis of post-marketing cases and the literature regarding SCAR."
Severe cutaneous adverse reactions (SCAR) are not listed in the CCDS (version 13, dated 28 June 2022) for Ad26.COV2.S or the current core Risk Management Plan (cRMP; version 6.0, dated 25October 2022).
A cumulative review of SCAR through 24February 2022 was previously conducted and included in the 3rd Ad26.COV2.S PBRER covering the reporting period of 25February 2022 to 24August 2022. The cumulative

analysis found insufficient information to associate SCAR or erythema multiforme (EM) with the Ad26.COV2.S vaccine. Current review will provide a high-level analysis of post-marketing cases and the literature regarding SCAR from 25February 2022 through 24February 2023 to bridge up to the data gap from the previous cumulative review for the same topic.

The 7 identified cases during the requested period are presented below:

Table 3: Cases Reporting Severe Cutaneous Adverse Reactions or Possible Severe Cutaneous Adverse Reactions From 25 February 2022 to 24 February 2023 (n=7)

AER Number Country Primary Source Age (Years)/Sex Medically Confirmed	MedDRA Preferred Terms of Interest/ Seriousness of EOI Outcome of EOI	TTO From Vaccination[a]	Medical History/ Concurrent Conditions	Cosuspect/ Concomitant Medications	Summary *MAH Comment*
[redacted] Spontaneous 41/Male No	Toxic skin eruption/ Serious Not resolved	NR	NR/ Drug hypersensitivity Hypertension Oral herpes	NR/ NR	This case concerned a patient who experienced toxic skin eruption within the same month of vaccination. Following vaccination, allergy tests confirmed known nickel allergy and known penicillin allergy. The face was the first to be affected, followed by the whole body, including arms and legs. The patient experienced itchiness. The patient had open sores on the hip, around both nipples, on both sides of the umbilicus, on the legs at the knee joint, and on the back. The patient's eczema worsened. The patient received treatment with topical cortisone, but it could not be tolerated. The patient also received treatment with betamethasone dipropionate/gentamicin sulfate, which provided relief for skin lesions, itching, and eczema. A diagnosis of toxic dermatitis was confirmed, and the patient was treated with doxycycline for 7 days, with good improvement. ***MAH Comment:*** *TTO and diagnostics in this case were unclear. This medically unconfirmed case lacked key details, including biopsy and laboratory test results, precluding a meaningful medical assessment.*
[redacted] Spontaneous 31/Male Yes	Drug reaction with eosinophilia and systemic symptoms/ Serious Resolving	6 weeks	Foetal exposure during pregnancy/ NR	NR/ Paracetamol	This literature case[b], also received through [redacted] concerned a patient who experienced seizures requiring intubation, 24 hours after the administration of Ad26.COV2.S. The patient was discharged on prophylactic levetiracetam and phenytoin. One month later, the patient was readmitted for worsening seizures and the workup revealed psychogenic seizures; levetiracetam and

					phenytoin were discontinued. Six weeks post-vaccination, the patient presented with diffuse erythematous morbilliform, intense pruritic rash, and high fever (103°F) for 5 days prior to presentation. The patient was treated with methylprednisolone and hydroxyzine. The rash improved in terms of redness, swelling, and itchiness, but continued to spread. Skin examination was normal except for morbilliform eruption with confluent erythema on the patient's chest, abdomen, back, penis, scrotum, and upper and lower extremities, as well as approaching erythroderma with pustule formation and palpable purpura on lower extremities. No mucosal or oral lesions were noted. The patient had bilateral inguinal, right cervical, and right axillary lymphadenopathy. Relevant laboratory tests revealed included elevated total white blood cell count of 19.57 (reference range 4.8 to 11.8×10^3/L), transaminitis with AST of 310 (reference range 0 to35 U/L) and ALT 996 (reference range 7 to45 U/L), CRP of 6.0 (reference range 0.0 to0.8 mg/dL), ESR 31 (reference range 0 to 9 mm/hr), and absolute eosinophil count of 1000 cells/µL of blood. An abdominal ultrasound revealed hepatomegaly with 1.6 cm hyperechoic right lobe lesion. A skin punch biopsy revealed spongiotic dermatitis with subcorneal pustules, along with superficial perivascular and mixed lymphocytic and neutrophilic infiltrate, with dermal edema and rare eosinophils. The patient was treated with triamcinolone ointment and prednisone. Upon treatment, the patient's rash and liver enzymes significantly improved.
					MAH Comment: *This case is confounded by the use of phenytoin[c]. Additionally, the authors remarked that after a thorough investigation, the rash was consistent with DRESS syndrome or a pustular drug eruption likely secondary to phenytoin or levetiracetam. The Sponsor agreed this causality assessment.*
[redacted] Spontaneous 32/Female No	Stevens-Johnson syndrome/ Serious Resolving	14 days	NR/ NR	NR/ NR	This case, reported from [redacted] concerned a patient who experienced Stevens-Johnson syndrome, 14 days after the administration of Ad26.COV2.S. ***MAH Comment:*** *While this case has plausible temporal relationship, this case lacked key details, including clinical signature presentation for SJS, medical history/concurrent conditions, biopsy, and laboratory test results, precluding a meaningful medical assessment.*
[redacted] Spontaneous 32/Female Yes	Stevens-Johnson syndrome/ Serious Resolving	3 days	NR/ NR	NR/ NR	This case, reported from [redacted], concerned a patient who experienced Stevens-Johnson syndrome, 3 days after the administration of Ad26.COV2.S. ***MAH Comment:*** *The TTO from the administration of Ad26.COV2.S of 3 days to the onset of Stevens-Johnson syndrome is atypical in this case[d]. This case lacked key details, including medical history/concurrent conditions, biopsy, and laboratory test results, precluding a meaningful medical assessment.*

[redacted] Spontaneous 41/Male No	Dermatitis bullous/ Serious Not resolved	31 days	Allergy to pollen and early bloomers/ NR	NR/ NR	This case, reported from EVHUMAN [redacted], concerned a patient who experienced bullous rash, 31 days after the administration of Ad26.COV2.S. ***MAH Comment**: The TTO from the administration of Ad26.COV2.S of 31 days to the onset of bullous dermatitis is atypical in this case[d]. Temporal relationship with Ad26.COV2.S is unlikely. Additionally, the patient had pre-existing allergy to pollen and early bloomers. The patient had simultaneous allergy aggravation at the same time as the bullous rash.*
[redacted] Spontaneous 48/Male Yes	Stevens-Johnson syndrome/ Serious Not resolved	2 weeks	NR/ Abstains from alcohol Hypertension Non-tobacco user Social anxiety disorder	NR/ Lisinopril Paroxetine	This case, reported from [redacted] concerned a patient who experienced Guillain-Barré syndrome, rash, and muscle weakness that progressed to inability to swallow and walk, 2 weeks after the administration of Ad26.COV2.S. During hospitalisation, a diagnosis of severe Stevens-Johnson type allergic reaction was confirmed. ***MAH Comment**: TTO is plausible in this case; however, the patient received lisinopril[e] and paroxetine[f] for unspecified durations, which were labeled for skin lesion complication*
[redacted] Spontaneous 66/Male No	Dermatitis bullous/ Serious Resolved	3 days	NR/ NR	NR/ NR	This medically unconfirmed case, reported from EVHUMAN [redacted] concerned a patient who experienced bullous eruption, 3 days after receiving Ad26.COV2.S. ***MAH Comment**: This medically unconfirmed case reported an atypical TTO of 3 days (typical onset of events 1 week after initial drug administration)[d]. Additionally, this case lacked key details, including medical history/concurrent condition, concomitant medication, biopsy/diagnostic test results, precluding a meaningful medical assessment.*

Key: AER=Adverse Event Report; ALT=Alanine Transaminase; AST=Aspartate Aminotransferase; COVID-19=Coronavirus Disease 2019; EOI=Event(s) of Interest; ESR=Erythrocyte Sedimentation Rate; EVHUMAN=EudraVigilance Human; MAH=Marketing Authorisation Holder; MedDRA=Medical Dictionary for Regulatory Activities; n=Number of Cases; NA=Not Applicable; NOS=Not Otherwise Specified; NR=Not Reported; NSAID=Nonsteroidal Anti-inflammatory Drug; PCR=Polymerase Chain Reaction; SAHPRA=South African Health Products Regulatory Authority; TTO=Time to Onset; VAERS=Vaccine Adverse Event Reporting System

a: TTO from the vaccination to the EOI onset has been presented.

b: Hanna M (2022), Yang S. COVID-19 vaccine: A Common Suspect but Rare Culprit in Drug Rash With Eosinophilia and Systemic Symptoms (DRESS) Syndrome. *Cureus* 2022;14(11): e31310.

c: Dilantin [package insert]. Morgantown, WV Mylan Pharmaceuticals;2023

d: Mockenhaupt M. Severe drug-induced skin reactions: clinical pattern, diagnostics and therapy. J Dtsch Dermatol Ges. 2009;7(2):142 160.

e: Lisinopril [package insert]. Las Vegas, NV Yiling Pharmaceutical Ltd; 2021

f: Paroxetine [package insert]. Somerset, NJ Solco Healthcare US, LLC; 2021

MAH Conclusion: Combined with the previous cumulative review and this interval analysis, the Company found insufficient information to associate SCAR or EM with the Ad26.COV2.S vaccine. The Company will continue to monitor cases involving SCAR and EM via routine pharmacovigilance activities.

Rapporteur assessment comment:

During the interval from 25 February 2022 to 24 February 2023, 7 cases of severe cutaneous adverse reaction were reported. All seven cases had confounding factors or lacking clinical information. Based on these cases, no additional actions are required, and continuation of routine monitoring will be sufficient.

2.2.3. Use With Concomitant Vaccination

During this reporting period, a total of 17 (6 medically confirmed and 11 medically unconfirmed) post-marketing sources (including spontaneous and solicited), initial, primary dose cases reporting the use with concomitant vaccination were identified. There were 9 serious and 8 nonserious cases which reported a total of 107 events (58 serious, 49 nonserious). Cumulatively, 114 (33 medically confirmed and 81 medically unconfirmed) post-marketing, primary dose cases reporting the use with concomitant

vaccination were identified. There were 53 serious and 61 nonserious cases which reported a total of 588 events (188 serious, 400 nonserious).

The most frequently reported coadministered vaccine type (both during the reporting period as well as cumulatively) was the influenza vaccine (interval n=14; cumulatively n=70).

Booster Dose
During this reporting period, a total of 34(8 medically confirmed and 26 medically unconfirmed) post-marketing, initial cases reported as booster were identified. There were 5serious and 29 nonserious cases which reported a total of 208 events (17 serious, 191 nonserious). Of these cases, 29 were heterologous and 5 were homologous. Cumulatively, 94 (16 medically confirmed and 78 medically unconfirmed) post-marketing cases reported as booster were identified. There were 31 serious and 63 nonserious cases which reported a total of 557 events (89 serious, 468 nonserious). Of these cases, 67 were heterologous and 27 were homologous.
The most frequently reported coadministered vaccine type (both during the reporting period as well as cumulatively) was the influenza vaccine (interval n=33; cumulatively n=89). Most of the cases reported reactogenicity related events.

Rapporteur assessment comment:

No new safety concern was detected for this item.

2.3. Evaluation of risks and new information

Effectiveness of Targeted follow-up questionnaires

In alignment with EU GVP Module V, the Company implemented specific follow-up questionnaires for certain events of special interest as part of its routine pharmacovigilance activities.

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 24August 2022, circulated on 04 April 2023, PRAC endorsed the discontinuation of targeted follow-up questionnaires (TFUQ) for TTS/VTE, VAED/VAERD and multisystemic inflammatory syndrome. These TFUQ will not be presented in this PBRER or in future PBRERs.

New Information on Important Identified Risks

Thrombosis With Thrombocytopenia Syndrome

Results/Discussion
During this reporting period, a total of 23 (18 medically confirmed and 5medically unconfirmed) initial, primary dose cases reporting TTS were retrieved. There were 22 serious and 1 nonserious case which reported a total of 67 EOI (63 serious, 4nonserious).
During this reporting period, only 1 medically confirmed, initial (no medically unconfirmed) case reported as booster was identified. This serious, heterologous case reported 3 serious EOI.

Post-marketing Sources (Including Spontaneous and Solicited) Cases
Primary Dose
During this reporting period, a total of 22 (17 medically confirmed and 5medically unconfirmed) post-marketing, initial, primary dose cases reporting TTS were retrieved. There were 22 serious cases which reported a total of 66 EOI (63 serious, 3 nonserious).

Cumulatively, 353 (273 medically confirmed and 80 medically unconfirmed) post-marketing, primary dose cases reporting TTS were retrieved. There were 352 serious and 1 nonserious case which reported a total of 1,405 EOI (1,388 serious, 17 nonserious).

Of these 22 cases received, the most frequently reported countries/territories of origin (n≥3) were the US (n=9), Greece (n=4), and followed by Canada and Germany (n=3 each). These cases concerned 7 males, 8 females, and 7 did not report sex. The age range was from 22 to 83 years.

Table 45: Frequency Distribution of MedDRA PTs in Post-marketing Primary Dose Cases Reporting Thrombosis With Thrombocytopenia Syndrome With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
Thrombosis with thrombocytopenia syndrome	11	0	98	0
Cerebral venous sinus thrombosis	5	0	89	0
Deep vein thrombosis	5	0	85	0
Transverse sinus thrombosis	4	0	16	0
Thrombotic thrombocytopenic purpura	4	0	15	0
Thrombocytopenia	4	0	199	0
Platelet count decreased	2	2	120	12
Pulmonary embolism	3	0	120	0
Superior sagittal sinus thrombosis	2	0	17	0
Portal vein thrombosis	2	0	26	0
Thrombosis	2	0	92	0
Jugular vein thrombosis	2	0	20	0
Sigmoid sinus thrombosis	2	0	6	0

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

a: The MedDRA PTs of interest with a frequency ≥2 have been presented and sorted by decreasing order for the reporting period (25 August 2022 to 24 February 2023). 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 period (25 August 2022 to 24 February 2023).

The EOI reported at a frequency ≥2 included thrombosis with thrombocytopenia syndrome (n=11), cerebral venous sinus thrombosis and deep vein thrombosis (n=5 each); transverse sinus thrombosis, thrombotic thrombocytopenic purpura, thrombocytopenia, and platelet count decreased (n=4 each); and pulmonary embolism (n=3); superior sagittal sinus thrombosis, portal vein thrombosis, thrombosis, jugular vein thrombosis, and sigmoid sinus thrombosis (n=2 each). The mean and median TTO were 111.3 and 23 days, respectively, and the range was from 10 to 467 days. Of the 66 EOI, outcomes were reported for 25 and are as follows: not resolved (n=15), resolving (n=7), and fatal (n=3). Of these 22 cases, for the reporting period, the Company identified these 15post-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 PRAC criteria.

Booster Dose

During this reporting period, 1 medically confirmed, post-marketing, initial, case reported as booster was identified. This heterologous case concerned a 33-year-old male from [redacted] who experienced the serious EOI of thrombosis with thrombocytopenia syndrome, cerebral venous sinus thrombosis, and haemorrhagic infarction. The TTO was not reported for any of the EOI and the reported outcomes were:

unknown (n=2) and not resolved (n=1).
Cumulatively, 7 medically confirmed (no medically unconfirmed) cases reported as booster were identified. There were 7 serious cases which reported a total of 16 serious EOIs. Of these cases, 2 were heterologous and 5 were homologous.

Clinical Trial Cases
During this reporting period, one clinical case (primary dose, no booster) was retrieved from Janssen Sponsored Studies and no cases were retrieved from Janssen Supported Clinical Studies.

Janssen Sponsored Clinical Studies
During this reporting period, one primary dose case reporting TTS was retrieved from a Janssen Sponsored Clinical Study. This case was reported from VAC31518COV3001 and concerned a male with an unknown age from [redacted] who experienced the nonserious event of thrombosis with thrombocytopenia syndrome. The TTO and outcome of the event were not reported. No cases reported as booster dose.

Janssen Supported Clinical Studies
During this reporting period, there were no cases were retrieved from Janssen Supported Clinical Studies.

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

Line Listings
Death: During the current reporting period (25 August 2022 to 24 February 2023), one fatal case reporting a fatal EOI was retrieved. This was a 28 year old German male who died due to TTS 10 days after vaccination with AD26.COV2.S.

MAH Conclusion
Based on the evaluation of the cases, and review of safety from other sources, the information is consistent with what is currently known about TTS.

Rapporteur assessment comment:

TTS is included in section 4.4 & 4.8 of the SmPC (and the PIL accordingly). It has been furthermore evaluated in a signal with EPITT 19689; EMEA/H/C/005737/II/0006/G; and in the MSSRs EMEA/H/C/005737/MEA/014.1 – 07. No additional new 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 period, a total of 42 (14medically confirmed and 28 medically unconfirmed) initial, primary dose cases reporting GBS were retrieved. All cases were serious and reported a total of 45serious EOI.
During this reporting period, a total of 7 (4medically confirmed and 3 medically unconfirmed) initial cases reported as booster were identified. All cases were serious and reported a total of 7 serious EOI. Of these cases, 5were homologous and 2 were heterologous.

Post-marketing Sources (Including Spontaneous and Solicited) Cases
Primary Dose
During this reporting period, a total of 41 (13 medically confirmed and 28 medically unconfirmed) post-marketing, initial, primary dose cases reporting GBS were retrieved. All cases were serious and reported

a total of 44 serious EOI.
Cumulatively, 625 (349 medically confirmed and 276 medically unconfirmed) post-marketing, primary dose cases reporting GBS were retrieved. All cases were serious and reported a total of 662 serious EOI. Of these 41 post-marketing primary dose cases received, the most frequently reported countries/territories of origin (n≥5) were the US (n=13), South Africa (n=9) and Germany (n=5). These cases concerned 22 males, 14 females, and 5 did not report sex. The age range was from 20 to 80 years.

Table 48: 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 Interval Reporting Period[a]		Number of Events Reported Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
Guillain-Barré syndrome	36	0	566	0
Chronic inflammatory demyelinating polyradiculoneuropathy	7	0	47	0
Demyelinating polyneuropathy	1	0	17	0

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: The MedDRA PTs of interest have been presented and sorted by decreasing order for the reporting period (25 August 2022 to 24 February 2023). 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 period (25 August 2022 to 24 February 2023).

The EOI included GBS (n=36), chronic inflammatory demyelinating polyradiculoneuropathy (n=7), and demyelinating polyneuropathy (n=1). The mean and median TTO were 53.2 and 18.0 days, respectively, and the range was from 0 to 324days. Of the 44 EOI, outcomes were reported for 29 and are as follows: not resolved (n=14), resolving (n=9), resolved (n=3), fatal (n=2), and resolved with sequelae (n=1).

Booster Dose
During this reporting period, a total of 7 (4 medically confirmed and 3 medically unconfirmed) initial, post-marketing cases reported as booster were identified. All cases were serious and reported a total of 7 serious EOI. Of these cases, 5were homologous and 2 were heterologous. Cumulatively, 17 (5medically confirmed and 12 medically unconfirmed) cases reported as booster were identified. All cases were serious and reported a total of 17 serious EOI. Of these cases, 10 were heterologous and 7 were homologous. Of these 7 post-marketing cases reported as booster, the most frequently reported country/territory of origin (n≥2) was Germany (n=2). These cases concerned 4females and 3 males. The age range was from 29 to 72 years.

Table 50: 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 Interval Reporting Period[a]		Number of Events Reported Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
Guillain-Barré syndrome	3	0	13	0
Demyelinating polyneuropathy	2	0	2	0
Chronic inflammatory demyelinating polyradiculoneuropathy	1	0	1	0
Miller Fisher syndrome	1	0	1	0

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

a: The MedDRA PTs of interest have been presented and sorted by decreasing order for the current reporting period (25 August 2022 to 24 February 2023).

b: For the cumulative column, the events were presented in decreasing order based on the event counts of the current reporting period (25 August 2022 to 24 February 2023).

The EOI included GBS (n=3), demyelinating polyneuropathy (n=2), and chronic inflammatory demyelinating polyradiculoneuropathy and Miller Fisher syndrome (n=1 each). The mean and median TTO were 144.8 and 109.0 days, respectively, and the range was from 17 to 344days. Of the 7 EOI, outcomes were reported for 5and are as follows: resolving (n=3), and fatal and resolved with sequelae (n=1 each).

Clinical Trial Cases

During this reporting period, 1 clinical case (primary dose, no booster) was retrieved from a Janssen Sponsored Clinical Study and no cases were retrieved from Janssen Supported Clinical Studies.

Janssen Sponsored Clinical Studies

During this reporting period, 1 primary dose case reporting GBS was retrieved from a Janssen Sponsored Clinical Study. This case was reported from VAC31518COV3001 and concerned a 66-year-old female from [redacted], who experienced a serious EOI of GBS. The TTO was not reported and the outcome was reported as resolved. No cases were reported as booster dose.

Literature ICSR

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

Line Listings

Death: During the current reporting period (25August 2022 to 24February 2023), a total of 5 fatal cases were retrieved. Of these cases, 3 reported a fatal EOI.

MAH 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 GBS.

Rapporteur assessment comment

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

Venous Thromboembolism

Venous thromboembolism (VTE) has been reclassified as an important identified risk in the EU RMP. According to the cRMP (version 5.0, dated 24May 2022), VTE is an important potential risk associated with the use of Ad26.COV2.S. However, on 10 May 2022, based on the evidence from post-marketing data sources, the Company reclassified VTE from an important potential risk to an important identified

risk. The cRMP (version 6.0, dated 25October 2022) applicable at the end of the reporting interval, was updated to reflect this change.

Results/Discussion

During this reporting period, a total of 104 (77 medically confirmed and 27 medically unconfirmed) initial, primary dose cases reporting VTE were retrieved. There were 93 serious and 11 nonserious cases which reported a total of 142 EOI (129 serious, 13 nonserious). During this reporting period, a total of 16 (13 medically confirmed and 3 medically unconfirmed) initial cases reported as booster were identified. There were 10 serious and 6 nonserious cases which reported a total of 18 EOI (12 serious, 6 nonserious). Of these cases, 11 were homologous and 5 were heterologous.

Post-marketing Sources (Including Spontaneous and Solicited) Cases

Primary Dose

During this reporting period, a total of 67 (40 medically confirmed and 27 medically unconfirmed) post-marketing, initial, primary dose cases reporting VTE were retrieved. There were 65 serious and 2 nonserious cases which reported a total of 101 EOI (99 serious, 2 nonserious). Cumulatively, 2,194 (1,499 medically confirmed and 695medically unconfirmed) post-marketing, primary dose cases reporting VTE were retrieved. There were 2,113 serious and 81 nonserious cases which reported a total of 2,842 EOI (2,732 serious, 110 nonserious).

Of these 67 post-marketing, primary dose cases received, the most frequently reported countries/territories of origin (n≥3) were the US (n=45), Germany (n=7), and followed by Canada, Greece, and South Africa (n=3 each). These cases concerned 31 males, 29 females, and 7 did not report sex. The age range was from 18 to 83 years.

Table 52: Frequency Distribution of MedDRA PTs 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 Period[a]		Number of Events Reported Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
Deep vein thrombosis	23	0	807	1
Pulmonary embolism	22	0	961	1
Cerebral venous sinus thrombosis	10	0	151	0

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

a: The MedDRA PTs of interest with a frequency ≥10 have been presented and sorted by decreasing order for the reporting period (25 August 2022 to 24 February 2023). 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 period (25 August 2022 to 24 February 2023).

The EOI reported at a frequency ≥10 included deep vein thrombosis (n=23), pulmonary embolism (n=22), and cerebral venous sinus thrombosis (n=10). The mean and median TTO were 161.1 and 61.0 days, respectively, and the range was from 0 to 653 days. Of the 101 EOI, outcomes were reported for 50 and are as follows: not resolved (n=20), resolving (n=10), resolved (n=9), fatal (n=8), and resolved with sequelae (n=3).

Booster Dose

During this reporting period, a total of 10 (7 medically confirmed and 3 medically unconfirmed) initial cases reported as booster were identified. All cases were serious and reported a total of 12 serious EOI. Of these cases, 7 were homologous and 3 were heterologous. Cumulatively, 70 (42 medically confirmed and 28 medically unconfirmed) cases reported as booster were identified. All cases were serious and reported a total of 83 serious EOI. Of these cases, 42 were homologous and 28 were heterologous. Of

these 10 post-marketing cases reported as booster, reported countries/territories of origin were the US (n=7), and followed by France, Germany, and South Africa (n=1 each). These cases concerned 5 males, 3 females, and 2 did not report sex. The age range was from 33 to 85 years.

Table 54: Frequency Distribution of MedDRA PTs in Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Venous Thromboembolism

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
Deep vein thrombosis	5	0	31	0
Pulmonary embolism	2	0	22	0
Pulmonary thrombosis	2	0	10	0
Central venous catheterisation	1	0	2	0
Cerebral venous sinus thrombosis	1	0	4	0
Retinal vein occlusion	1	0	2	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 period (25 August 2022 to 24 February 2023). 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 period (25 August 2022 to 24 February 2023).

The EOI included deep vein thrombosis (n=5), and pulmonary embolism and pulmonary thrombosis (n=2 each), and central venous catheterisation, cerebral venous sinus thrombosis, and retinal vein occlusion (n=1 each). The mean and median TTO were 337.7 and 357.5 days, respectively, and the range was from 29 to 493 days. Of the 12 EOI, outcomes were reported for 4and are as follows: resolved (n=3) and not resolved (n=1).

Clinical Trial Cases

During this reporting period, a total of 43 clinical cases (37 primary dose and 6 booster) were retrieved from Janssen Sponsored and Janssen Supported Clinical Studies.

Janssen Sponsored Clinical Studies

During this reporting period, a total of 36 primary dose cases reporting VTE were retrieved from Janssen Sponsored Clinical Studies. Of the 36 cases, 19 were from VAC31518COV3001, 16 from VAC31518COV3009, and 1 from VAC31518COV1001. These 36 cases reported 40 EOI (29 serious, 11 nonserious). Of these 36 cases, the most frequently reported countries/territories of origin (n≥3) were the US (n=19), and followed by Belgium, South Africa, Spain, and the UK (n=3 each). These cases concerned 22 males and 14females. The age range was from 26 to 89 years. The EOI reported at a frequency ≥2 included pulmonary embolism (n=17), deep vein thrombosis (n=12), and superficial vein thrombosis and venous thrombosis limb (n=2 each). The mean and median TTO were 520.0 and 549.0 days, respectively, and the range was from 57 to 760 days. The reported outcomes of the EOI are as follows: resolved (n=16), resolving (n=12), not resolved (n=8), and resolved with sequelae (n=3), and fatal (n=1). During this reporting period, a total of 6 cases reported as booster were retrieved from Janssen Sponsored Clinical Studies.

Of the 6 cases, 3 each were reported from VAC31518COV3009 and VAC31518COV3001. These 6 cases reported 6 nonserious EOI. The reported countries/territories of origin were Brazil (n=2), and followed by Argentina, Belgium, the UK, and the US (n=1 each). These cases concerned 3 males and females. The age range was from 55 to 78 years. The most frequently reported EOI (n ≥4) included deep vein thrombosis. The mean and median TTO were 402.3 and 415.5days, respectively, and the range was from

174to 612 days. The reported outcomes of the EOI are as follows: resolved (n=4), and not resolved and resolving (n=1 each).

Janssen Supported Clinical Studies Cases

During this reporting period, 1 primary dose cases reporting VTE was retrieved from a Janssen Supported Clinical Study. This case was reported from [redacted] and concerned a male of unspecified age from [redacted], who experienced a serious EOI of pulmonary embolism. The TTO was 61 days, and the reported outcome was resolving. No cases reported as booster dose were retrieved.

Literature ICSR

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

Line Listings

Death: During the current reporting period (25August 2022 to 24February 2023), a total of 9 fatal cases were retrieved. Of these cases, 7 reported a fatal EOI.

MAH Discussion and Conclusion

Since VTE is now an important identified risk, the change in strategy has resulted in reduced number of cases retrieved for both interval and cumulative periods.

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.

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 reporting interval, the cRMP version 6.0, 25October 2022 was updated accordingly.

There is no additional new safety concern detected with VTE.

New Information on Important Potential Risks

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

Results/Discussion

Primary Dose

There were no initial, primary dose cases retrieved from the search of the Company global safety database during this reporting period. Cumulatively, 1 medically confirmed, post-marketing, primary dose case reporting VAED, including VAERD was retrieved. This case reported 1 serious EOI of VAED, 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 period. 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 period.

Line Listings

Death: During the current reporting period (25 August 2022 to 24 February 2023), no fatal cases were retrieved.

MAH Conclusion

Based on the evaluation of the cases, and review of safety from other sources, no new information was received on the topic of VAED, including VAERD.

Rapporteur assessment comment:

No new safety concern is detected here.

Immune Thrombocytopenia

Results/Discussion

During this reporting period, a total of 84 (71 medically confirmed and 13 medically unconfirmed) initial, primary dose cases reporting thrombocytopenia were retrieved. There were 44 serious and 40 nonserious cases which reported a total of 90 EOI (43 serious, 47 nonserious). During this reporting period, a total of 15medically confirmed (no medically unconfirmed) initial cases reported as booster were identified. There were 3 serious and 12 nonserious cases which reported a total of 15 EOI (3 serious, 12 nonserious). Of these cases, 4 was heterologous and 11 were homologous.

Post-marketing Sources (Including Spontaneous and Solicited) Cases

Primary Dose

During this reporting period, a total of 39 (26 medically confirmed and 13 medically unconfirmed) post-marketing, initial, primary dose cases reporting thrombocytopenia were retrieved. All cases were serious and included a total of 44 EOI (40 serious; 4nonserious). Out of these 39 cases, 20 cases were assessed as ITP cases per ASH case definition. Cumulatively, 841 (610 medically confirmed and 231 medically unconfirmed) post-marketing, primary dose cases reporting thrombocytopenia were retrieved. There were 722 serious and 119 nonserious cases which reported a total of 987 EOI (836 serious, 151 nonserious). Out of 841 cases, 421 cases were assessed as ITP cases per ASH case definition. Of these 20 cases received, the most frequently reported countries/territories of origin were the US (n=13), Germany (n=3), and followed by France and Italy (n=1 each). These cases concerned 8 males, 10 females, and 2 cases who did not report sex. The age range was from 40 to 83 year.

Table 57: Frequency Distribution of MedDRA PTs of Interest in Post-marketing Primary Dose Cases Assessed as Immune Thrombocytopenia With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
Platelet count decreased	8	3	119	41
Thrombocytopenia	7	0	143	0
Immune thrombocytopenia	5	0	82	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 period (25 August 2022 to 24 February 2023). 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 period (25 August 2022 to 24 February 2023).

The EOI included platelet count decreased (n=11), thrombocytopenia (n=7), immune thrombocytopenia (n=5). The mean and median TTO were 181.7 and 55days, respectively, and the range was from 0 to 611 days. Of the 23 EOI, outcomes were reported for 12 and are as follows: not resolved (n=10), resolved with sequelae (n=1), and resolved (n=1).

Booster Dose

During this reporting period, 3 medically confirmed (no medically unconfirmed) initial cases reported as booster were identified. These 3 serious cases reported a total of 3 serious EOI. Out of these 3 cases, 1 case was assessed as ITP per ASH case definition. This post-marketing, heterologous case concerned a 64-year-old male from [redacted] who experienced a serious EOI of immune thrombocytopenia. The TTO was not reported, and outcome was reported as resolved. Cumulatively, 23 (13 medically confirmed and 10 medically unconfirmed) cases reported as booster were identified. There were 20 serious and 3 nonserious cases which reported a total of 24 EOI (15serious, 9 nonserious). Of these cases, 11 were heterologous and 12 were homologous. Out of 23 cases, 17 cases were assessed as ITP cases per ASH case definition.

Clinical Trial Cases

During this reporting period, a total of 57 clinical cases (45primary and 12 booster) were retrieved from Janssen Sponsored Clinical Studies. No cases were retrieved from Janssen Supported Clinical Studies.

Janssen Sponsored Clinical Studies

During this reporting period, a total of 45 primary dose cases reporting thrombocytopenia were retrieved from Janssen Sponsored Clinical Studies. Of the 45 cases, 37 were reported from VAC31518COV3001, 5 from VAC31518COV3003, 2 from VAC31518COV3009, and 1 from VAC18193RSV2008. These 45 cases reported 46 EOI (43 nonserious; 3 serious). Of these 45cases, the most frequently reported countries/territories of origin (n≥3) were the US (n=28), Brazil (n=8), and Colombia (n=3). These cases concerned 34males and 11 females. The age range was from 21 to 74 years. The EOI included thrombocytopenia (n=40), platelet count decreased (n=5), and thrombosis with thrombocytopenia syndrome (n=1). The mean and median TTO were 354 and 350 days, respectively, and the range was from 0 to 713 days. Of the 46 EOI, outcomes were reported for 42 and are as follows: resolved (n=32), resolving (n=6), and not resolved (n=4). During this reporting period, a total of 12 cases reported as booster were retrieved from Janssen Sponsored Clinical Studies. Nine were reported from VAC31518COV3001, 2 from VAC31518COV3009, and 1 from VAC31518COV3005. These 12 cases reported 12 nonserious EOI. Of these 12 cases, the countries/territories of origin were the US (n=6), Brazil (n=3), Colombia (n=2), and Chile (n=1). These cases concerned 9 males and 3 females. The age range was from 55 to 73 years. The EOI included thrombocytopenia (n=11) and platelet count decreased (n=1). The mean and median TTO were 71.1 and 18 days, respectively, and the range was from 0 to 531 days. The outcomes were reported as resolved (n=10) and resolving (n=2).

Janssen Supported Clinical Studies Cases

During this reporting period, there were no cases retrieved from Janssen Supported Clinical Studies.

Literature ICSR

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

Line Listings

Death: During the current reporting period (25August 2022 to 24February 2023), a total of3 fatal cases were retrieved. Of these cases, 1 reported a fatal EOI.

MAH 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 immune thrombocytopenia.

Rapporteur assessment comment:

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

New Information on Other Identified Risks not Categorised as Important

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

New Information on Other Potential Risks not Categorised as Important

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

New Information on Missing Information

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 24August 2022, circulated on 04April 2023, PRAC indicated that, "The section 'Update on special patient populations', i.e. pregnancy/breastfeeding; Use in immunocompromised patients; Use in patients with autoimmune or inflammatory disorders; Use in frail patients with comorbidities (e.g., chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders should only be included and discussed in the PSUR if the reporting pattern changes and/or there is a safety issue/signal".
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. MAH has included separate appendices for each topic.

Rapporteur assessment comment

In line with the last PSUR, the MAH will only present data on topics included under missing information if there is a safety issue/signal. No such has been presented. No new safety concern is detected.

2.4. Adverse events of special interest

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 24August 2022, circulated on 04 April 2023, PRAC endorsed the discontinuation of presentation of the following separate AESI within the current and future PBRERs: acute aseptic arthritis, acute kidney failure, acute renal failure; convulsions, disseminated intravascular coagulation, sensorineural hearing loss, and transverse myelitis. These topics will not be discussed within this PBRER or in future PBRERs.

Cardiac Disorders

Cardiac Inflammatory Disorder, Including Myocarditis and Pericarditis

On 14 February 2023 a signal was identified for cardiac inflammatory disease (including myocarditis and pericarditis) with the use Ad26.COV2.S based on a request from the US FDA to perform a review of the topic.

Additional information on the cumulative analysis of myocarditis/pericarditis can be found in the section late breaking information above.

Cardiomyopathy

Results/Discussion

During this reporting period, a total of 4 (3 medically confirmed and 1 medically unconfirmed) initial, primary dose cases reporting cardiomyopathy were retrieved. All cases were serious and reported a total of 5serious EOI.

During this reporting period, 1 medically unconfirmed, initial case reported as booster was identified. This serious case was heterologous and reported 1 serious EOI. Post-marketing Sources (Including Spontaneous and Solicited) Cases

Primary Dose

During this reporting period, a total of 2 (1 medically confirmed and 1 medically unconfirmed) post-marketing, initial, primary dose cases reporting cardiomyopathy were retrieved. Both cases were serious and reported a total of 3 serious EOI. Cumulatively, 73 (47 medically confirmed and 26 medically unconfirmed) post-marketing, primary dose cases reporting cardiomyopathy were retrieved. All cases were serious and reported a total of 82 EOI (79 serious, 3 nonserious).

Of these 2 post-marketing, primary dose cases retrieved, the only reported country/territory of origin was [redacted] These cases concerned 1 female and 1 male, aged 62 and 22 years, respectively. The EOI included ejection fraction decreased, hypertrophic cardiomyopathy, and ischaemic cardiomyopathy (n=1 each). The mean and median TTO were 208.3 and 307.0 days, respectively, and the range was from 11 to 307. The reported outcomes of the EOI were resolved (n=2) and not resolved (n=1).

Booster Dose

During this reporting period, 1 medically unconfirmed, post-marketing, initial case reported as booster was identified. This heterologous case concerned a 43-year-old male from [redacted] who experienced a serious EOI of cardiomyopathy. The TTO was 143 days, and the outcome was reported as not resolved.

Cumulatively, 5(1 medically confirmed and 4medically unconfirmed) cases reported as booster were identified. All cases were serious and reported a total of 5serious EOI. Of these cases, 4were heterologous and 1 was homologous.

Clinical Trial Cases

During this reporting period, a total of 2 clinical cases (both primary dose and no booster) were retrieved from Janssen Sponsored Clinical Studies and no cases were retrieved from Janssen Supported Clinical Studies.

Janssen Sponsored Clinical Studies

During this reporting period, a total of 2 primary dose cases reporting cardiomyopathy were retrieved from Janssen Sponsored Clinical Studies. Of the 2 cases, 1 each was reported from VAC31518COV3009 and VAC31518COV3001. These 2 cases reported 2 serious EOI. Of these 2 cases, the only reported country/territory of origin was [redacted] These cases concerned 1 female and 1 male, aged 78 and 66 years, respectively.

The EOI included cardiac amyloidosis and ischaemic cardiomyopathy (n=1 each). The TTO was only reported for 1 case as 479 days. The reported outcomes were not resolved and resolving (n=1 each).

During this reporting period, no cases reported as booster were retrieved from Janssen Sponsored Clinical Studies.

Literature ICSR

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

Line Listings

Death: During the current reporting period (25August 2022 to 24February 2023), no fatal cases were retrieved.

O/E Analysis Results

Table 58: Cardiomyopathy: Restricted O/E and Sensitivity Analysis Results (Cumulative Through 24 February 2023)

	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	9.00	0.69	(0.32, 1.31)	2.33	(1.07, 4.42)
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)

Table 58: Cardiomyopathy: Restricted O/E and Sensitivity Analysis Results (Cumulative Through 24 February 2023)

	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)

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.

MAH Discussion and conclusion

Of the 5primary and booster dose cases received in this interval, there was an approximately even distribution of males and females. Ages reported ranged from 22 to 78, with 3 cases concerning patients 62 years and older. Four of the cases reported concurrent conditions that confound assessment, and these concurrent conditions included hypertension, blood cholesterol increased, hyperlipidaemia, cardiac conditions (atrial flutter, atrial fibrillation, coronary artery disease, congestive cardiac failure, myocardial infarction, ischaemic cardiomyopathy), carcinoma, drug abuse, and nicotine dependence. TTO ranged from 11 days to 479 days, with 3 of the cases reporting TTO of 143 days or more. 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 cardiopathy 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 cardiopathy as an AESI.

Rapporteur assessment comment:

As seen already in earlier PSURs and MSSRs (detailed investigation of this term performed in MSSR6) O/E ratios are significantly increased with emphasis on the US data. No additional new concern is raised with the presentation of the current interval data.

Coronary Artery Disease (Including Acute Myocardial Infarction)

Results/Discussion

During this reporting period, a total of 102 (74 medically confirmed and 28 medically unconfirmed) initial, primary dose cases reporting CAD, including acute MI were retrieved. There were 99 serious and 3 nonserious cases, which reported a total of 116 EOI (113 serious, 3 nonserious).

During this reporting period, a total of 16 (7 medically confirmed and 9 medically unconfirmed) initial cases reported as booster were identified. All cases were serious and reported a total of 20 serious EOI. Of these cases, 11 were homologous, and 5were heterologous.

Post-marketing Sources (Including Spontaneous and Solicited) Cases

Primary Dose

During this reporting period, a total of 49 (21 medically confirmed and 28 medically unconfirmed) post-marketing, initial, primary dose cases reporting CAD, including acute MI were retrieved. There were 47 serious and 2 nonserious cases which reported a total of 60 EOI (58 serious, 2 nonserious).

Cumulatively, 774 (371 medically confirmed and 403 medically unconfirmed) post-marketing, primary dose cases reporting CAD, including acute MI were retrieved. There were 768 serious and 6 nonserious cases which reported a total of 964EOI (951 serious, 13 nonserious).

The EOI reported (n≥3) included myocardial infarction (n=18), acute myocardial infarction (n=13), angina pectoris (n=11), and coronary artery disease and troponin increased (n=3 each). The mean and median TTO were 151.0 and 88.0 days, respectively, and the range was from 0 to 578 days. Of the 60 EOI, outcomes were reported for 32 and are as follows: not resolved (n=10), resolved (n=8), fatal (n=7), resolved with sequelae (n=5), and resolving (n=2).

Booster Dose

During this reporting period, a total of 14 (5 medically confirmed and 9 medically unconfirmed) initial cases reported as booster were identified. All cases were serious and reported a total of 18 serious EOI. Of these cases, 10 were homologous and 4 were heterologous.

Cumulatively, 58 (19 medically confirmed and 39 medically unconfirmed) cases reported as booster were identified. All cases were serious and reported a total of 69 serious EOI. Of these cases, 31 were heterologous and 27 were homologous.

Of these 14 post-marketing cases reported as booster, the countries/territories of origin were the US (n=9) and Germany (n=5). These cases concerned 8 males, 5females, and 1 did not report sex. The age range was from 35 to 81 years.

The EOI reported (n≥2) included myocardial infarction (n=8), angina pectoris (n=4), and acute myocardial infarction and coronary artery disease (n=2 each). The mean and median TTO were 214.7 and 251.0 days, respectively, and the range was from 0 to 429 days. Of the 18 EOI, outcomes were reported for 8 and are as follows: resolved with sequelae (n=4), fatal (n=2), and not resolved and resolved (n=1 each).

Clinical Trial Cases

During this reporting period, a total of 55clinical cases (53 primary dose and 2 booster) were retrieved from Janssen Sponsored and Janssen Supported Clinical Studies.

Janssen Sponsored Clinical Studies

During this reporting period, a total of 52 primary dose cases reporting CAD, including acute MI were retrieved from Janssen Sponsored Clinical Studies. Of the 52 cases, 29 were reported from VAC31518COV3001, 22 from VAC31518COV3009, and 1 from VAC31518COV2008. These 52 cases reported 55 EOI (54 serious, 1 nonserious). Of these 52 cases, the most frequently reported countries/territories of origin (n≥5) were the US (n=16), Brazil (n=8), and followed by Belgium and Columbia (n=5each). These cases concerned 38 males and 14females. The age range was from 44to 94years.

The EOI reported (n≥5) included acute myocardial infarction (n=18), coronary artery disease (n=14), and angina unstable and myocardial infarction (n=5each). The mean and median TTO were 539.0 and 538.5days, respectively, and the range was from 186 to 752 days. The reported outcomes were as follows: resolved (n=28), resolving (n=14), fatal and not resolved (n=5each), and resolved with sequelae (n=3).

During this reporting period, a total of 2 cases reporting booster doses were retrieved from a Janssen Sponsored Clinical Study. Both cases were reported from VAC31518COV3001. These 2 cases reported 2 serious EOI. The countries/territories of origin reported were [redacted] and [redacted] (n=1 each). Both cases concerned males, aged 62 and 69 years, respectively.

The EOI included acute coronary syndrome and acute myocardial infarction (n=1 each). The reported TTO were 114 and 192 days. The reported outcomes were as follows: resolving and not resolved (n=1 each).

Janssen Supported Clinical Studies Cases

During this reporting period, 1 primary dose case reporting CAD, including acute MI was retrieved from a Janssen Supported Clinical Study. This case was reported from [redacted] and concerned a 72-year-old female from [redacted] who experienced a serious EOI of acute myocardial infarction. The reported TTO was 265days, and the outcome was reported as resolving. During this reporting period, no cases reported as booster were retrieved from Janssen Supported Clinical Studies.

Literature ICSR

ICSR literature cases received during the current reporting period were reviewed, and no information was identified that would change the information known about CAD, including acute MI.

Line Listings

Death: During the current reporting period (25August 2022 to 24February 2023), a total of 16 fatal cases were retrieved. Of these cases, 14 reported a fatal EOI.

O/E Analysis Results

Since the previous PBRER DLP (24August 2022), the broad O/E ratio has remained <1 in the US and EU for both age groups. A restricted O/E analysis with sensitivity analysis was not required.

MAH Conclusion

Based on the evaluation of the cases, and review of safety from other sources, the information retrieved during the reporting period remains consistent with previous observations regarding CAD, including acute MI following Ad26.COV2.S. No safety concern has been identified and based on the overall reporting of cases within the expected range, the Company proposes to monitor CAD, including acute MI through regular pharmacovigilance activities.

Rapporteur assessment comment: No new safety concern is detected with CAD and MI.

Nervous System Disorders

Encephalitis (Including Acute Disseminated Encephalomyelitis and Meningoencephalitis)

Results/Discussion

During this reporting period, a total of 5 (2 medically confirmed and 3 medically unconfirmed) initial, primary dose cases reporting encephalitis, including ADEM and meningoencephalitis, were identified. All 5cases were serious and reported a total of 5serious EOI.

During this reporting period, 1 medically confirmed, initial case reported as booster was identified. This serious case was homologous and reported 1 serious EOI.

Post-marketing Sources (Including Spontaneous and Solicited) Cases

Primary Dose

During this reporting period, a total of 4(1 medically confirmed and 3 medically unconfirmed) post-marketing, initial, primary dose cases reporting encephalitis, including ADEM and meningoencephalitis were retrieved. All 4cases were serious and reported a total of 4serious EOI. Cumulatively, 88 (59 medically confirmed and 29 medically unconfirmed) post-marketing, primary dose cases reporting encephalitis, including ADEM and meningoencephalitis were identified. All cases were serious and reported a total of 92 serious EOI.

In these 4post-marketing primary dose cases received during this reporting period, the reported countries/territories of origin were the US (n=2), and followed by Denmark and South Africa (n=1 each). These cases concerned 3 females and 1 male. The age range was from 24to 46 years.

The EOI included encephalitis autoimmune (n=2), and acute disseminated encephalomyelitis and encephalitis (n=1 each). Of the 4cases, the TTO was reported only for 1 case as 5days. Of the 4EOI, outcomes were reported for 3 and are as follows: not resolved, resolved, and resolved with sequelae (n=1 each).

Booster Dose

During this reporting period, 1 medically confirmed, post-marketing, initial case reported as booster was identified. This homologous case concerned a 47-year-old male from [redacted] who experienced a serious EOI of encephalitis autoimmune. The TTO and outcome of the EOI were not reported.

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 period, 1 clinical case (primary dose and no booster) was retrieved from a Janssen Sponsored Clinical Study and no cases were retrieved from Janssen Supported Clinical Studies.

Janssen Sponsored Clinical Studies

During this reporting period, 1 primary dose case reporting encephalitis, including ADEM and meningoencephalitis, was retrieved from a Janssen Sponsored Clinical Study. It was confirmed that the

patient was randomised to placebo group. The case is in the process of being updated and the change will be reflected in the next PBRER. This case was reported from VAC31518COV3009 and concerned a 75-year-old female from [redacted] who experienced a serious EOI of encephalitis autoimmune. The TTO was not reported, and the outcome was reported was resolving.

Literature ICSR

ICSR literature cases received during the current reporting period 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 period (25August 2022 to 24February 2023), 1 fatal case with no fatal EOI was retrieved.

O/E Analysis Results

Table 63: Encephalitis, ADEM Alone: Restricted O/E and Sensitivity Analysis Results (Cumulative Through 24 February 2023)

		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	21.00	0.15	(0.09, 0.22)	2.52	(1.56, 3.86)
ADEM	US	18 to 59	7.65	0.61	(0.26, 1.22)	3.17	(1.34, 6.33)
	EU	18 to 59	5.00	0.35	(0.11, 0.81)	1.80	(0.58, 4.20)

Key: ADEM=Acute Disseminated Encephalomyelitis; CI=Confidence Interval; AESI=Adverse Event of Special Interest; EU=European Union; EOI=Event(s) of Interest; LB=Lower Bound; O/E=Observed Versus Expected; PE=Point Estimate; RP=Reporting Percentage; US=United States

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

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

Encephalitis

The US restricted sensitivity analysis showed an O/E ratio of>1 for the 18 to 59 age group only. This O/E ratio was statistically significant above 1 (lower bound of 95% confidence interval >1). The lower bound of the 95% confidence interval for the 18 to 59 age group was <1 in the previous interval. 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).

ADEM

The US restricted sensitivity analysis showed an O/E ratio of >1 for the 18 to 59 age group. This O/E ratio was statistically significant above 1 (lower bound of 95% confidence interval >1). The EU restricted sensitivity analysis showed an O/E ratio of >1 for the 18 to 59 age group. This O/E ratio was not statistically significant above 1 (lower bound of 95%confidence interval <1).

MAH Conclusion

Based on the evaluation of the cases, and review of safety from other sources, the information retrieved during the reporting period 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:

This AESI has been evaluated in depth in earlier SSRs and no new additional safety concern is detected during this PSUR interval.

Multiple Sclerosis (Including Optic Neuritis)

Results/Discussion

During this reporting period, a total of 6 (3 medically confirmed and 3 medically unconfirmed) initial, primary dose cases reporting multiple sclerosis, including optic neuritis, were retrieved. All 6 cases were serious and reported a total of 6 serious EOI.

During this reporting period, a total of 3 (1 medically confirmed and 2 medically unconfirmed) initial cases reported as booster were identified. All 3 cases were serious and reported a total of 3 serious EOI reporting multiple sclerosis, including optic neuritis. Of these cases, 2 cases were heterologous and 1 was homologous.

Post-marketing Sources (Including Spontaneous and Solicited) Cases

Primary Dose

During this reporting period, a total of 5 (2 medically confirmed and 3 medically unconfirmed) post-marketing, initial, primary dose cases reporting multiple sclerosis, including optic neuritis, were retrieved. All 5cases were serious and reported a total of 5serious EOI.

Cumulatively, 72 (35 medically confirmed and 37 medically unconfirmed) post-marketing, primary dose cases reporting multiple sclerosis, including optic neuritis, were retrieved. All 72 cases were serious and reported a total of 74serious EOI.

Of these 5 post-marketing primary dose cases received, the countries/territories of origin were the US (n=2), and followed by Belgium, Czech Republic, and Germany (n=1 each). These cases concerned 2 males, 2 females, and 1 did not report sex. The age range was from 33 to 62 years.

The EOI included multiple sclerosis and multiple sclerosis relapse (n=2 each), and optic neuritis (n=1). The mean and median TTO were 98 and 101.5days, respectively, and the range was from 25 to 164days. Of the 5EOI, outcomes were reported for 3 and are as follows: resolved with sequelae (n=2) and not resolved (n=1).

Booster Dose

During this reporting period, a total of 3 (1 medically confirmed and 2 medically unconfirmed) post-marketing, initial cases reported as booster were identified. All 3 cases were serious and reported a total of 3 serious EOI. Of these cases, 2 were heterologous and 1 was homologous. Cumulatively, 8 (4 medically confirmed and 4 medically unconfirmed) post-marketing cases reported as booster were identified. All 8 cases were serious and reported a total of 10 serious EOI.

Of these cases, 5 were heterologous and 3 were homologous.

Of the 3 initial post-marketing cases reported as booster, the countries/territories of origin were Germany (n=2) and Spain (n=1). These cases concerned 2 females and 1 male. The age range was from 25 to 71 years.

The EOI included leukoencephalopathy, optic neuritis, and relapsing-remitting multiple sclerosis (n=1 each). The mean and median TTO were 89.3 and 32 days, respectively, and the range was from 7 to 229 days. The outcomes were reported as not resolved (n=2) and resolved with sequelae (n=1).

Clinical Trial Cases

During this reporting period, a total of 1 clinical case (primary dose, no booster) was retrieved from a Janssen Sponsored Clinical Study and no cases were retrieved from Janssen Supported Clinical Studies.

Janssen Sponsored Clinical Studies

During this reporting period, 1 primary dose case reporting multiple sclerosis, including optic neuritis, was retrieved from a Janssen Sponsored Clinical Study. This case was reported from [redacted] This case reported 1 serious EOI optic neuritis with a TTO of 5days in a 26-year-old female from [redacted] The outcome was reported as resolved.

During this reporting period, no cases reported as booster were identified from Janssen Sponsored Clinical Studies.

Literature ICSR

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

Line Listings

Death: During the current reporting period (25August 2022 to 24February 2023), no fatal cases were retrieved.

O/E Analysis Results

Since the previous PBRER DLP (24August 2022), the broad O/E ratio has remained <1 in the US and EU for both age groups. A restricted O/E analysis with sensitivity analysis was therefore not required.

MAH Conclusion

Based on the evaluation of the cases, and review of safety from other sources, the information retrieved during the reporting period remains consistent with previous observations regarding multiple sclerosis, including optic neuritis 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 cases of multiple sclerosis, including optic neuritis as an AESI.

Rapporteur assessment comment:

This AESI has been evaluated in depth in the MSSRs 6-9 including a time frame up to March 2022 and no new safety information has been identified in these reports. No additional safety concern is raised in this PSUR. A close monitoring of this term as suggested by the MAH is endorsed.

Narcolepsy

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 24August 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 period, a total of 24 (1 medically confirmed and 23 medically unconfirmed) initial, primary dose cases reporting narcolepsy were retrieved. There were 5 serious and 19 nonserious cases which reported a total of 24 EOI (3 serious, 21 nonserious).

During this reporting period, a total of 14 (2 medically confirmed and 12 medically unconfirmed) initial cases reported as booster were identified. There were 4 serious and 10 nonserious cases which reported a total of 14EOI (2 serious, 12 nonserious). Of these cases, 9 were heterologous and 5 were homologous.

Post-marketing Sources (Including Spontaneous and Solicited) Cases

Primary Dose

During this reporting period, a total of 24 (1 medically confirmed and 23 medically unconfirmed) post-marketing, initial, primary dose cases reporting narcolepsy were retrieved. There were 5serious and 19 nonserious cases which reported a total of 24EOI (3 serious, 21 nonserious).

Cumulatively, 586 (79 medically confirmed and 507 medically unconfirmed) post-marketing, primary dose cases reporting narcolepsy were retrieved. There were 188 serious and 398 nonserious cases which reported a total of 594 EOI (94 serious, 500 nonserious). Of these 24 post-marketing primary dose cases received, the most frequently reported countries/territories of origin (n≥5) were Germany (n=9) and followed by Belgium and the US (n=5each). These cases concerned 13 males, 8 females, and 3 did not report sex. The age range was from 20 to 63 years.

The EOI included sleep disorder (n=17) and hypersomnia (n=7). The mean and median TTO were 35.6 days and 1 day, respectively, and the range was from 0 to 426 days. Of the 24EOI, outcomes were reported for 19 and are as follows: resolving (n=7), not resolved (n=5), resolved with sequelae (n=4), and resolved (n=3).

Booster Dose

During this reporting period, a total of 14 (2 medically confirmed and 12 medically unconfirmed) post-marketing, initial cases reported as booster were identified. There were 4 serious and 10 nonserious cases which reported a total of 14 EOI (2 serious, 12 nonserious). Of these cases, 9 were heterologous and 5 were homologous.

Cumulatively, 46 (5 medically confirmed and 41 medically unconfirmed) post-marketing cases reported as booster were identified. There were 15serious and 31 nonserious cases which reported a total of 47 EOI (6 serious, 41 nonserious). Of these cases, 26 were heterologous and 20 were homologous.

Of these 14 post-marketing cases reported as booster, the most frequently reported countries/territories of origin (n≥2) were Germany (n=7), the US (n=3) and Canada (n=2). These cases concerned 7 females, 5 males, and 2 did not report sex. The age range was from 26 to 84years.

The EOI included sleep disorder (n=10), hypersomnia (n=3), and narcolepsy (n=1). The mean and median TTO were 87.9 and 48 days, respectively, and the range was from 0 to 274days. Of the 14EOI, outcomes were reported for 9 and are as follows: resolving (n=4), resolved with sequelae (n=3), and not resolved (n=2).

Among 14 post-marketing cases, 1 heterologous booster case reported narcolepsy as an EOI. This was not a medically confirmed case and diagnosis of narcolepsy was not valid.

Clinical Trial Cases

During this reporting period, there were 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 period.

Line Listings

Death: During the current reporting period (25 August 2022 to 24 February 2023), no fatal cases were retrieved.

O/E Analysis Results

Table 70: 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 Count[a]	O/E Ratio (95% CI)[b] (PE, 100% RP)		O/E Ratio (95% CI)[b] (LB, 50% RP)	
EU	18 to 59	107.34	0.84	(0.69, 1.02)	3.23	(2.65, 3.91)
	≥60	21.62	2.97	(1.85, 4.51)	25.05	(15.63, 38.06)

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).

MAH Conclusion

Based on the evaluation of the cases, and review of safety from other sources, the information retrieved during the reporting period 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:

During this reporting period, a total of 24 (1 medically confirmed and 23 medically unconfirmed) post-marketing, initial, primary dose cases reporting narcolepsy were retrieved. The EOI included sleep disorder (n=17) and hypersomnia (n=7). Among 14 post-marketing cases, 1 heterologous booster case reported narcolepsy as an EOI. This was not a medically confirmed case and diagnosis of narcolepsy was not valid.

No new safety concern is detected here.

Vascular Disorders

Cerebrovascular Events

Results/Discussion

During this reporting period, a total of 152 (93 medically confirmed and 59 medically unconfirmed) initial, primary dose cases reporting cerebrovascular events were retrieved. There were 151 serious and 1 nonserious case which reported a total of 199 cerebrovascular events (198 serious, 1 nonserious).

During this reporting period, a total of 26 (13 medically confirmed and 13 medically unconfirmed) initial cases reported as booster were identified. There were 24 serious and 2 nonserious cases which reported a total of 34 cerebrovascular events (32 serious, 2 nonserious). Of these cases, 7 were heterologous and 19 were homologous.

Post-marketing Sources (Including Spontaneous and Solicited) Cases

Primary Dose

During this reporting period, a total of 109 (50 medically confirmed and 59 medically unconfirmed) post-marketing, initial, primary dose cases reporting cerebrovascular events were retrieved. All these cases serious and reported a total of 152 serious cerebrovascular events.

Cumulatively, 1,622 (935 medically confirmed and 687 medically unconfirmed) post-marketing primary dose cases reporting cerebrovascular events were retrieved. There were 1,620 serious and 2 nonserious cases which reported a total of 2,235 cerebrovascular events (2,231 serious, 4nonserious).

Of these 109 cases received, the most frequently reported countries/territories of origin (n≥8) were the US (n=66), Germany (n=13), and the Philippines (n=8). These cases concerned 49 females, 47 males, and 13 did not report sex. The age range was from 22 to 93 years.

The cerebrovascular events (≥11) included cerebrovascular accident (n=50), hemiparesis (n=16), and cerebral venous sinus thrombosis (n=11). The mean and median TTO were 136.7 days and 41 days respectively and the range was from the same day to 608 days. Of the 152 cerebrovascular events, outcomes were reported for 87 and are as follows: not resolved (n=35), fatal (n=22), resolved (n=17), resolving (n=12), and resolved with sequelae (n=1).

Information on Patients ≤40 Years of Age (Including Fatalities)

During this reporting period, a total of 2 fatal (1 primary dose and 1 case reported as booster) were reported in patients ≤40 years of age. In addition, a total of 18 non-fatal (17 primary dose and 1 case reported as booster) cases were reported in patients ≤40 years of age.

One booster case involved a fatal haemorrhagic event. Two of the non-fatal cases involved a haemorrhagic event (primary doses).

Both of the fatal cases reported a TTO within the 28-day risk window. Assessment of 1 of the cases (primary dose) was confounded by the patient's concurrent condition. The remaining case did not report medical history and/or concurrent disease that would confound the case, and included relevant details on medical history, concomitant medications, and diagnostic test results.

Of the 18 non-fatal cases, the EOI was outside the 28-day risk window in 6 cases (all primary dose). Of the remaining 12 cases, assessment in 5 (4 primary dose and 1 case reported as booster) were confounded by the patients' medical history and/or concurrent diseases. Of the remaining 7 cases, 7 (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 period did not identify evidence suggestive of cerebrovascular events being causally associated with Ad26.COV2.S.

Booster Dose

During this reporting period, a total of 25(12 medically confirmed and 13 medically unconfirmed) initial cases reported as booster were identified. There were 24 serious and 1 nonserious case which reported a total of 33 cerebrovascular events (32 serious, 1 nonserious). Of these cases, 7 were heterologous and 18 were homologous.

Cumulatively, 66 (36 medically confirmed and 30 medically unconfirmed) cases reported as booster were identified. There were 65 serious cases and 1 nonserious case which reported a total of 86 cerebrovascular events (84 serious, 2 nonserious). Of these cases, 22 were heterologous and 44were homologous.

Of these 25 post-marketing cases reported as booster, the most frequently reported countries/territories of origin (n≥3) were the US (n=15) and followed by Brazil and Germany (n=3 each). These cases concerned 11 females, 11 males, and 3 did not report sex. The age range was from 23 to 92 years.

The cerebrovascular events (n≥2) included cerebrovascular accident (n=15), hemiparesis, ischaemic stroke, and transient ischaemic attack (n=3 each), and cerebral thrombosis (n=2). The mean and median TTO were 137.4 days and 48 days respectively and the range is from same day to 419 days. Of the 33 cerebrovascular events, outcomes were reported for 16 and are as follows: fatal (n=6), not resolved and resolved (n=4each) and resolved with sequelae and resolving (n=1 each).

Clinical Trial Cases

During this reporting period, a total of 44 clinical cases (43 primary dose and 1 booster) were retrieved from Janssen Sponsored and Janssen Supported Clinical Studies.

Janssen Sponsored Clinical Studies

During this reporting period, a total of 41 primary dose cases reporting cerebrovascular events were retrieved from Janssen Sponsored Clinical Studies. Of the 41 cases, 21 were from VAC31518COV3001 and 20 from VAC31518COV3009 These 41 cases reported 45cerebrovascular events (44 serious, 1 nonserious). Of these 41 cases, the most frequently reported countries/territories (n≥9) of origin were the US (n=18) and Philippines (n=9). These cases concerned 23 males and 18 females. The age range was from 43 to 91 years.

The cerebrovascular events (n≥3) included cerebrovascular accident and ischaemic stroke (n=9 each), transient ischaemic attack (n=7), and cerebral infarction, and haemorrhagic stroke (n=3 each). The mean and median TTO were 527.8 and 540 days, respectively and the range was from 142 to 750 days. The outcomes were reported for all the 45 cerebrovascular events and are as follows: resolved (n=27), resolving (n=9), fatal(n=4), not resolved (n=3), and resolved with sequelae (n=2).

During this reporting period, 1 case reported as booster was identified from a Janssen Sponsored Clinical Study. This case was from VAC31518COV3009 and concerned a 60-year-old male from [redacted] This nonserious case reported 1 nonserious cerebrovascular event of cerebral infarction. The reported TTO was 609 days, and the event outcome was reported as resolving.

Janssen Supported Clinical Studies Cases

During this reporting period, a total of 2 primary dose cases reporting cerebrovascular events were retrieved from Janssen Supported Clinical Studies. Of the 2 cases, 1 was from [redacted] and the other from [redacted] These 2 cases reported 2 serious cerebrovascular events. The reported countries/territories of origin were [redacted] and [redacted] These cases concerned 1 male and 1 female. The reported age was 28 years and 71 years.

The cerebrovascular events included cerebrovascular accident and subarachnoid haemorrhage (n=1 each). The mean and median TTO were 158.5 days, and the range was from 34to 283 days. The outcomes were reported as fatal and resolved (n=1 each).

There were no booster cases identified from Janssen Supported Clinical Studies.

Literature ICSR

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

Line Listings

Death: During the current reporting period (25August 2022 to 24 February 2023), a total of 27 fatal cases were retrieved. Of these cases, 22 reported a fatal cerebrovascular event.

O/E Analysis Results

Cerebrovascular Events -Haemorrhagic

Table 75: Cerebrovascular Events - Haemorrhagic: Restricted O/E and Sensitivity Analysis Results (Cumulative Through 24 February 2023)

		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	9.39	0.35	(0.16, 0.66)	3.07	(1.43, 5.76)
		30 to 39	13.58	0.37	(0.20, 0.63)	4.85	(2.63, 8.21)
		40 to 49	31.63	0.67	(0.46, 0.95)	10.85	(7.41, 15.35)
		50 to 64	62.28	0.43	(0.33, 0.56)	7.13	(5.47, 9.14)
		65 to 74	35.15	0.3	(0.21, 0.42)	3.31	(2.31, 4.60)
		≥75	32.29	0.2	(0.14, 0.29)	2.53	(1.73, 3.57)
	Male	18 to 29	1.66	0.03	(0.00, 0.14)	0.28	(0.02, 1.12)
		30 to 39	9.71	0.16	(0.08, 0.30)	1.99	(0.94, 3.70)
		40 to 49	20.87	0.28	(0.17, 0.43)	4.57	(2.83, 7.00)
		50 to 64	63.88	0.3	(0.23, 0.38)	4.63	(3.56, 5.91)
		65 to 74	31.12	0.2	(0.14, 0.28)	1.82	(1.24, 2.58)
		≥75	24.34	0.18	(0.11, 0.26)	2.43	(1.56, 3.61)
EU	Female	18 to 29	5.27	2.07	(0.70, 4.72)	11.73	(3.95, 26.81)
		30 to 39	2.21	0.6	(0.08, 2.06)	2.52	(0.36, 8.63)
		40 to 49	11.77	1.21	(0.62, 2.13)	3.69	(1.89, 6.49)
		50 to 64	13.81	0.41	(0.22, 0.69)	1.09	(0.59, 1.83)
	Male	18 to 29	6.00	2.03	(0.74, 4.41)	10.59	(3.89, 23.05)
		30 to 39	7.00	0.86	(0.35, 1.78)	2.86	(1.15, 5.89)
		40 to 49	4.44	0.27	(0.08, 0.67)	0.75	(0.22, 1.84)

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 76: Cerebrovascular Events – Non-Haemorrhagic: Restricted O/E and Sensitivity Analysis Results (Cumulative Through 24 February 2023)

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	10.67	0.29	(0.14, 0.51)	3.76	(1.85, 6.78)
		30 to 39	17.97	0.21	(0.12, 0.33)	4.33	(2.57, 6.85)
		40 to 49	42.07	0.32	(0.23, 0.43)	7.59	(5.47, 10.26)
		50 to 64	73.16	0.16	(0.12, 0.20)	4.59	(3.60, 5.77)
		65 to 74	38.54	0.09	(0.07, 0.13)	1.28	(0.91, 1.75)
		≥75	50.48	0.09	(0.07, 0.12)	1.13	(0.84, 1.48)
	Male	18 to 29	4.59	0.12	(0.04, 0.30)	1.35	(0.41, 3.27)
		30 to 39	13.63	0.12	(0.07, 0.21)	2.01	(1.09, 3.40)
		40 to 49	19.78	0.11	(0.07, 0.17)	1.99	(1.21, 3.08)
		50 to 64	86.67	0.13	(0.11, 0.17)	2.49	(2.00, 3.08)
		65 to 74	36.04	0.07	(0.05, 0.10)	0.8	(0.56, 1.11)
		≥75	26.30	0.06	(0.04, 0.09)	0.9	(0.59, 1.31)
EU	Female	18 to 29	6.27	0.67	(0.25, 1.45)	2.35	(0.88, 5.05)
		30 to 39	6.21	0.37	(0.14, 0.80)	1.05	(0.39, 2.25)
	Male	18 to 29	9.30	0.89	(0.41, 1.67)	3.05	(1.41, 5.72)
		30 to 39	13.23	0.79	(0.42, 1.34)	2.24	(1.20, 3.82)

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 (Days 1 to 28) only.

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

The US restricted sensitivity analysis showed an O/E ratio of >1 for all female and all male age groups except the male 65 to 74 and ≥75 age groups. Of these, the O/E ratio was statistically significant above 1 (lower bound of 95% confidence interval >1) for all the female age groups except the 65 to 74 and the ≥ 75 age groups and for all the male age groups concerned except the 18 to 29 age group.

The EU restricted sensitivity analysis showed an O/E ratio of >1 for 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. Since the previous PBRER DLP (24August 2022), for the EU female 30 to 39 age group, the restricted sensitivity O/E ratio showed an increase from <1 to >1. The O/E ratio was not statistically significant above 1 (lower bound of 95% confidence interval >1).

MAH Conclusion

During the reporting period, 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.

Rapporteur assessment comment:

During the interval reporting period of 25 August 2022 to 24 February 2023, 152 (93 medically confirmed and 59 medically unconfirmed) initial, primary dose cases reporting cerebrovascular events were identified. Of these, 151 were serious. Forty-one of the cases were reported from Janssen clinical studies, most of them from US (n=18), and 109 were from post-marketing sources. The EOI (≥11) included cerebrovascular accident (n=50), cerebral venous sinus thrombosis (n=11), and hemiparesis (n=16). The mean and median TTO were 136.7 and 41 days, respectively.

During the reporting period, 25 (12 medically confirmed and 13 medically unconfirmed) initial cases reported as a booster dose were identified, 24 of them were serious and reported a total of 33 EOI (32 serious; 1 nonserious). Of these cases, 7 were heterologous and 18 were homologous. One of the cases were reported from a Janssen clinical study. Most of the post-marketing cases were reported from US.

During the reporting interval, a signal on haemorrhagic cerebrovascular events was opened by the MAH based on disproportionalities in VigiBase. The outcome should be provided in the next PSUR **(see section 4)**.

Death

As per PRAC confirmation received in the PRAC FAR (PRAC AR 2022) for the Ad26.COV2.S PBRER (25August 2021 to 24February 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 the fourth PBRER dated 25 August 2022 to 24 February 2023 and in future PBRERs.

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.

Data on long term efficacy are still missing. Currently there are no new data on efficacy that raises a concern.

4. Benefit-risk balance

JCOVDEN (Ad26.COV2.S, COVID-19 Vaccine Janssen) is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older. The use of this vaccine should be in accordance with official recommendations.

The vaccine is based on the initial Wuhan strain and has not been updated. Serious ADRs have been identified post marketing; occurring at different frequencies including TTS (very rare), venous thromboembolism (rare), ITP (not known), GBS (very rare), transverse myelitis (not known), CLS (not known) and cutaneous small vessel vasculitis, which have been reflected in the SmPC/PIL and evaluated mainly during the last PSUR intervals within a number of other procedures. Various events are still under further monitoring. These observations have led to the currently very limited use of this vaccine within the EU.

Assessment of the data within the current PSUSA does not alter the balance between benefits and risks, and thus the benefit/risk balance remains unchanged.

5. Rapporteur Request for supplementary information

None

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Periodic Benefit Risk Evaluation Report

JNJ-78436735 (Ad26.COV2.S) Vaccine

Note: This report may contain unblinded clinical trial adverse event data

PERIOD COVERED BY THIS REPORT:
25 August 2022 to 24 February 2023

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EXECUTIVE SUMMARY

Introduction

This Periodic Benefit Risk Evaluation Report (PBRER) for JNJ-78436735 (Ad26.COV2.S), herein referred to as Ad26.COV2.S, summarises the safety data obtained by the Company from worldwide sources for the reporting period of 25 August 2022 to 24 February 2023. 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, guidance from the EMA on the Consideration on Core Requirements for PSURs of Coronavirus Disease 2019 (COVID-19) vaccines,[1] and guidance outlined in EMA's Consideration on Core Requirements for Risk Management Plan of COVID-19 vaccine.[2] The International Birth Date of Ad26.COV2.S is based on the first regulatory approval in Bahrain on 25 February 2021.

Ad26.COV2.S is indicated for active immunisation for the prevention of COVID-19 in adults greater than or equal to 18 years of age. Ad26.COV2.S is administered as a colourless to slightly yellow, clear to very opalescent single dose suspension, for intramuscular injection. A booster dose (second dose) may be administered as a homologous booster dose intramuscularly at least 2 months after the primary vaccination in individuals 18 years of age and older. A booster dose may also be administered as a heterologous booster following the completion of a primary messenger ribonucleic acid COVID-19 vaccination, an adenoviral vector-based COVID-19 vaccine or an inactivated whole-virion COVID-19 vaccine. The dosing interval for the heterologous booster dose is the same as the dosing interval authorised for the booster dose of the vaccine 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 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 104 countries/territories and import licences have been granted in 20 countries/territories worldwide (see Section 2, Worldwide Marketing Authorisation Status).

Exposure

Cumulative Exposure in Clinical Trials

Overall, an estimated 82,249 healthy subjects have been enroled in the Ad26.COV2.S clinical programme, of which approximately 68,714 subjects received Ad26.COV2.S in the Company-sponsored interventional clinical trials. Of these, 675 subjects were exposed to Ad26.COV2.S in the Phase 1 trials, 935 subjects to

[1] EMA/362988/2021 (dated 08 July 2021)

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

Ad26.COV2.S in a Phase 1/2a trial, 1,883 subjects to Ad26.COV2.S in the Phase 2 trials, 537 subjects to Ad26.COV2.S in the Phase 2a trial, and over 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 752,163 subjects to Ad26.COV2.S in the other studies (see Section 5.1, Cumulative Subject Exposure in Clinical Trials).

Cumulative and Interval Patient Exposure from Marketing Experience

Cumulative

A total of 611,193,650 doses of Ad26.COV2.S vaccine were distributed and 53,047,996 were administered worldwide from launch to 28 February 2023.

A total of 3,132,632 subjects were administered the homologous Ad26.COV2.S vaccine booster dose in South Africa, South Korea, and the United States (US) from launch to 28 February 2023.

Interval

A total of 120,564,550 doses of Ad26.COV2.S vaccine were distributed and 366,693 were administered worldwide from 01 September 2022 to 28 February 2023.

A total of 152,796 subjects were administered the homologous Ad26.COV2.S vaccine booster dose in South Africa, South Korea, and the US from 01 September 2022 to 28 February 2023 (see Section 5.2, Cumulative and Interval Patient Exposure From Marketing Experience).

Summary of the Overall Benefit-Risk Analysis Evaluation

Despite increasing numbers of vaccinated subjects, the ongoing SARS-CoV-2 pandemic remains a public health issue of international concern. The emergence of new virulent lineages has fuelled the need for highly effective preventive measures. Effective and safe COVID-19 vaccines remain a pivotal tool for controlling the disease.

Ad26.COV2.S demonstrated high efficacy against severe/critical disease caused by SARS CoV2 and protection against hospitalisation and death in clinical trial settings. Analysis of spontaneous reports of vaccination failure did not show trends for lack of efficacy. Altogether, the totality of data 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 28 February 2023, over 53,047,996 doses of the Ad26.COV2.S vaccine have been administered (CDC 2023, ECDC 2023, KDCA 2023). 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.

Based on the newly published estimates of Janssen vaccine primary and booster doses duration of effectiveness during Omicron predominance, Janssen COVID-19 vaccine continues to provide protection during Omicron predominance. The newly identified risk of myocarditis and pericarditis does not change the existing established benefit/risk profile. The marketing authorisation holder will continue to monitor the benefit-risk profile of Ad26.COV2.S as Omicron predominance wanes and when other variants, perhaps with different transmission intensity and severity characteristics, are circulating.

Taking into account the safety data cumulatively, the overall benefit-risk assessment remains favourable for Ad26.COV2.S when used as recommended in the currently approved indications for both primary and booster active immunisation to prevent COVID-19 infection caused by SARS-COV-2 virus in adults ≥18 years of age. 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 (see Section 18.2, Benefit-Risk Analysis Evaluation).

Actions Taken and Proposed for Safety Reasons

On 23 December 2022, France's Agence Nationale de Sécurité du Médicament et des Produits de Santé requested the continual receipt of information on French fatal pregnancy/breastfeeding cases.

On 14 February 2023, the United State Food and Drug Administration requested addition of myocarditis and pericarditis to the Warnings and Precautions section of the Emergency Use Authorisation Fact Sheet.

Details on the actions can be found in Section 3, Actions Taken in the Reporting Interval for Safety Reasons.

Conclusions

During the period of this update, including late-breaking information, myocarditis and pericarditis have been considered adverse drug reactions and important identified risks associated with Ad26.COV2.S. Consequently, an update to the safety sections of the prescribing information as well as risk management plan will be implemented accordingly. 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
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CIOMS	Council for International Organisation of Medical Sciences
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
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
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
MAH	Marketing Authorisation Holder (Company)
MCL	Mean Cycle Length
MedDRA	Medical Dictionary for Regulatory Activities
MERS-CoV	Middle East Respiratory Syndrome Related Coronavirus
mRNA	Messenger Ribonucleic Acid
N/A	Not Applicable
NEC	Not Elsewhere Classified
O/E	Observed versus Expected
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 are synonymous
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 Neutralization 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 period.
Developmental International Birth Date	The date of first approval (or authorisation) to conduct an interventional clinical trial in any country/territory.
Follow-up case	A case for which additional information was received in the period covered by this PBRER.
International Birth Date	The date of first marketing authorisation for any product containing the active substance granted to any company in any country/territory in the world.
Interventional	Clinical trials that may involve the following elements: • Those that involve the use of a medicinal product outside of the terms of the marketing authorisation (eg, new indications, dosage range, frequency, combinations) • Those that influence the freedom of choice for a specific treatment option by the treating health professional (eg, the assignment of a patient to a particular treatment strategy is decided in advance by the protocol) • Those that clearly involve additional diagnostic and/or monitoring procedures that are not part of routine clinical practice.
Latency	Unless otherwise defined, latency is the time from initiation of therapy to onset of adverse event.
Marketing Authorisation Holder (Company)	The generic term "Company-sponsored study" is used throughout the document in lieu of the term "MAH-sponsored study" as the J&J entity acting as study sponsor or as MAH may be different. The term "MAH-sponsored study" is retained for the appendices to keep the terminology in line with the GVP module VII titles for appendices.
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 period, 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 period of 25 August 2022 to 24 February 2023. 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), guidance from the EMA on the Consideration on Core Requirements for PSURs of Coronavirus Disease 2019 (COVID-19) vaccines,[3] and guidance outlined in EMA's Consideration on Core Requirements for Risk Management Plan (RMP) of COVID-19 vaccine.[4] The International Birth Date (IBD) of Ad26.COV2.S is based on the first regulatory approval in Bahrain on 25 February 2021.

Ad26.COV2.S is indicated for active immunisation for the prevention of COVID-19 in adults greater than or equal to 18 years of age. Ad26.COV2.S is 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 acid 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.

[3] EMA/362988/2021 (dated 08 July 2021)

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

2. WORLDWIDE MARKETING AUTHORISATION STATUS

The IBD for Ad26.COV2.S is 25 February 2021 based on the first authorisation in Bahrain. The indications and the approved doses can be found in Section 1, Introduction.

Ad26.COV2.S is authorised in 104 countries/territories and import licenses have been granted in 20 countries/territories worldwide (see Table 1 and Table 2). In addition, Ad26.COV2.S obtained an Emergency Use Listing by the World Health Organization (WHO).

Table 1: List of Countries/Territories Where Ad26.COV2.S is Authorised (n=104)

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

Key: n=Number

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

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

Key: n=Number

3. ACTIONS TAKEN IN THE REPORTING INTERVAL FOR SAFETY REASONS

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

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

Date	Country/Territory	Issue	Action Taken
23 December 2022	France	ANSM request to continue receiving information about pregnancy/breastfeeding cases with fatal outcome which occurred in France with Janssen COVID-19 vaccine.	The National PV Monitoring was re-opened regarding the pregnancy and breastfeeding cases with fatal outcome which occurred in France with the Janssen COVID-19 vaccine.
14 February 2023	United States	Externally identified significant safety issue.	US FDA requested an update to the Janssen COVID-19 vaccine EUA fact sheet to include a new Warnings and Precautions for myocarditis and pericarditis. HA notifications in other countries/territories were made in line with local requirements.

Key: ANSM=Agence Nationale de Sécurité du Médicament et des Produits de Santé; COVID-19=Coronavirus Disease 2019; EUA=Emergency Use Authorisation; FDA=Food and Drug Administration; HA=Health Authority; PV=Pharmacovigilance; US=United States

4. CHANGES TO REFERENCE SAFETY INFORMATION

The CCDS contains the Company Core Safety Information (CCSI). The CCDS in effect at the end of the reporting period is dated June 2022. No significant changes were made to the CCDS (ie, CCSI) within the reporting interval.

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

5. ESTIMATED EXPOSURE AND USE PATTERNS

5.1. Cumulative Subject Exposure in Clinical Trials

Overall, an estimated 82,249 healthy subjects have been enroled in the Ad26.COV2.S clinical programme, of which approximately 68,714 subjects received Ad26.COV2.S in the Company-sponsored interventional clinical trials (see Table 4). Of these, 675 subjects were exposed to Ad26.COV2.S in the Phase 1 trials,[5] 935 subjects to Ad26.COV2.S in a Phase 1/2a

[5] Trials included VAC31518COV1002, VAC31518COV1003, and VAC18193RSV2008.

trial,[6] 1,883 subjects to Ad26.COV2.S in the Phase 2 trials,[7] 537 subjects to Ad26.COV2.S in the Phase 2a trial,[8] and over 64,684 subjects to Ad26.COV2.S in the Phase 3 trials.[9]

Additionally, 16,142 subjects were exposed to Ad26.COV2.S in the pre-approval access programmes,[10] and 752,163 subjects to Ad26.COV2.S in the other studies.[11]

Table 4: Estimated Cumulative Subject Exposure From Clinical Trials

Treatment	Number of Subjects
Ad26.COV2.S	68,714
Comparator	N/A
Placebo	39,413

Key: Ad26.COV2.S=Adenovirus type 26.Coronavirus 2.Spike; N/A=Not Applicable
Note: Number of subjects exposed to at least 1 study vaccine, recorded in the study databases up to cut-off date (24 February 2023).
Trials included: VAC31518COV1001, VAC31518COV1002, VAC31518COV1003, VAC31518COV2001, VAC31518COV2004, VAC31518COV2008, VAC31518COV3001, VAC31518COV3003, VAC31518COV3005, VAC31518COV3006, VAC31518COV3009, and VAC18193RSV2008.
The number of subjects exposed to study vaccine in blinded study (Ad26.COV2.S for VAC18193RSV2008) are estimates.
A total of 25,878 subjects (506 subjects from Trial VAC31518COV1001; 0 subjects from Trial VAC31518COV1002; 0 subjects from Trial VAC31518COV1003; 150 subjects from Trial VAC31518COV2001; 0 subjects from Trial VAC31518COV2004; 0 subjects from Trial VAC31518COV2008; 16,047 subjects from Trial VAC31518COV3001; 0 subjects from Trial VAC31518COV3003; 781 subjects from Trial VAC31518COV3005; 151 subjects from Trial VAC31518COV3006; 8,243 subjects from Trial VAC31518COV3009; and 0 subjects from Trial VAC18193RSV2008) that received a regimen with both Ad26.COV2.S and placebo, subjects are counted for both Ad26.COV2.S and placebo.

Table 5 and Table 6 show cumulative subject exposure by age and sex, and by race from completed clinical trials, respectively.

Table 5 Cumulative Subject Exposure to Ad26.COV2.S from Completed Clinical Trials by Age and Sex

Age Range (Years)[a]	Number of Subjects		
	Male	Female	Total
12-17	10	20	30
18-40	347	255	602
41-64	120	85	205
65-75	137	104	241
>75	27	12	39
Total	**641**	**476**	**1,117**

[6] Trial included VAC31518COV1001.
[7] Trials included VAC31518COV2004, VAC31518COV2008, and VAC31518COV3006.
[8] Trial included VAC31518COV2001.
[9] Trials included VAC31518COV3001, VAC31518COV3003, VAC31518COV3005, and VAC31518COV3009.
[10] Programs included VAC31518COV4006 and VAC31518COV4007.
[11] Studies included COV-BOOST (VAC31518COV2009), VAC31518COV2012, VAC31518COV2016 (AUR1-8-341), VAC31518COV3012 (Sisonke [Together]), VAC31518COV3018, VAC31518COV3021 (Sisonke Boost Open-label Study [SISONKE2]), VAC31518COV4012, and DMID 21-0012.

Table 5 Cumulative Subject Exposure to Ad26.COV2.S from Completed Clinical Trials by Age and Sex

Age Range (Years)[a]	Number of Subjects		
	Male	Female	Total

Note: Completed trials included VAC31518COV1002, VAC31518COV1003 and VAC31518COV2001.
a: Data from completed trials as of 24 February 2023.

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

Race Group[a]	Number of Subjects
American Indian or Alaska Native	3
Asian	208
Black or African American	7
Native Hawaiian or other Pacific Islander	0
White	874
Multiple	13
Unknown	6
Not reported	6
Missing	0
Total	**1,117**

Note: Completed Trials included VAC31518COV1002, VAC31518COV1003 and VAC31518COV2001.
a: Data from completed trials as of 24 February 2023.

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 period (01 September 2022 to 28 February 2023) is provided in Table 7.

Table 7: Subject Exposure to the Ad26.COV2.S Vaccine During the Reporting Period (01 September 2022 to 28 February 2023)

Region/Country/Territory	Number of Distributed Doses[a]	Number of Administered Doses[b,c]
EEA		
Austria	0	443
Belgium	0	854
Bulgaria	0	4,167
Croatia	825,600	605
Cyprus	48,000	89
Czechia	0	844
Estonia	0	418
France	0	1,764
Germany	0	3,460
Greece	0	2,639
Hungary	0	3,727
Iceland	0	20
Ireland	0	4,549
Italy	0	867
Latvia	0	16,563
Lithuania	0	179
Malta	110,400	23
Norway	0	74
Poland	0	67,734
Portugal	0	2,528
Romania	0	3,837
Slovakia	0	1,406
Spain	0	874
ROW		
Afghanistan	2,901,600	NR
Algeria	223,200	NR
Cameroon	1,058,400	NR
Central African Republic	1,058,400	NR
Chad	2,570,400	NR
Congo, (Kinshasa)	14,332,800	NR
Côte D'ivoire	501,600	NR
Djibouti	86,400	NR
Gambia	230,400	NR
Ghana	1,051,200	NR
Grenada	2,400	NR
Guinea	1,514,400	NR
Guinea-Bissau	230,400	NR
Haiti	122,400	NR
Kenya	199,200	NR
Lesotho	439,200	NR
Liberia	79,200	NR
Madagascar	1,252,800	NR
Malawi	2,345,600	NR
Mali	1,881,550	NR
Mauritania	201,600	NR
Namibia	26,400	NR
Niger	2,268,000	NR
Nigeria	26,006,400	NR
Saint Lucia	4,800	NR
Saint Vincent and Grenadines	7,200	NR
Senegal	451,200	NR
Sierra Leone	1,370,400	NR

Table 7: Subject Exposure to the Ad26.COV2.S Vaccine During the Reporting Period (01 September 2022 to 28 February 2023)

Region/Country/Territory	Number of Distributed Doses[a]	Number of Administered Doses[b,c]
South Africa	11,376,000	139,858
South Korea	0	1,511
South Sudan	3,069,600	NR
Sudan	10,584,000	NR
Uganda	7,567,200	NR
Ukraine	1,101,600	NR
United Republic of Tanzania	19,936,750	NR
Uzbekistan	1,003,150	NR
Zambia	2,524,700	NR
US	***0***	***107,660***
Total	**120,564,550**	**366,693**

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 28 February 2023.

A total of 120,564,550 doses[12] of Ad26.COV2.S vaccine were distributed worldwide from 01 September 2022 to 28 February 2023. In the current reporting period, there has been an approximately 6% decrease in distributed doses worldwide compared to the previous reporting period (01 March 2022 to 31 August 2022).

A total of 366,693 doses[12] of Ad26.COV2.S vaccine were administered worldwide from 01 September 2022 to 28 February 2023. In the current reporting period, there has been an approximately 62% decrease in administered doses worldwide compared to the previous reporting period (01 March 2022 to 31 August 2022).

Cumulative Exposure Estimates

The cumulative subject exposure for the Ad26.COV2.S vaccine from launch to 28 February 2023 is provided in Table 8.

[12] There has been a decrease in both the number of distributed and administered doses due to a decrease in demand for the vaccine in both the US and in other countries/territories.

Table 8: Cumulative Subject Exposure to the Ad26.COV2.S Vaccine (Launch to 28 February 2023)

Region/Country/Territory	Number of Distributed Doses[a]	Number of Administered Doses[b,c]
EEA		
Austria	1,292,400	368,393
Belgium	629,200	428,570
Bulgaria	1,777,300	530,431
Croatia	1,135,150	204,713
Cyprus	190,500	31,033
Czechia	547,200	413,752
Denmark	1,198,800	46,004
Estonia	110,800	79,350
Finland	68,400	NR
France	3,416,300	1,090,592
Germany	7,818,150	3,753,219
Greece	1,521,600	786,023
Hungary	4,309,200	345,528
Iceland[d]	33,500	54,323
Ireland	281,500	241,646
Italy	2,370,000	1,483,503
Latvia	767,800	294,214
Liechtenstein	NR	264
Lithuania[d]	287,200	295,937
Luxembourg	80,200	41,489
Malta	226,800	32,421
Netherlands	2,464,800	755,524
Norway	403,900	7,399
Poland	15,523,300	2,984,415
Portugal[d]	993,600	1,139,518
Romania	4,080,300	2,068,803
Slovakia	475,200	186,591
Slovenia	230,400	135,699
Spain	2,659,000	1,981,696
Sweden	55,200	NR
ROW		
Afghanistan	17,596,850	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	4,057,250	NR
Burundi	302,400	NR
Cambodia	1,060,100	NR
Cameroon	4,800,650	NR
Canada	168,000	NR
Central African Republic	3,074,700	NR
Chad	10,364,050	NR
Colombia	11,504,800	NR
Congo (Brazzaville)	2,696,600	NR
Congo, (Kinshasa)	22,965,600	NR
Côte D'ivoire	5,774,200	NR

Table 8: Cumulative Subject Exposure to the Ad26.COV2.S Vaccine (Launch to 28 February 2023)

Region/Country/Territory	Number of Distributed Doses[a]	Number of Administered Doses[b,c]
Djibouti	446,400	NR
Egypt	15,513,450	NR
Ethiopia	41,759,750	NR
Gabon	866,400	NR
Gambia	777,600	NR
Ghana	9,840,000	NR
Grenada	2,400	NR
Guinea	2,594,400	NR
Guinea-Bissau	1,598,400	NR
Guyana	96,000	NR
Haiti	348,000	NR
Jamaica	216,000	NR
Kenya	14,944,250	NR
Lao PDR	1,771,200	NR
Lebanon	336,000	NR
Lesotho	1,472,250	NR
Liberia	3,211,200	NR
Madagascar	4,790,750	NR
Malawi	5,913,950	NR
Mali	3,333,550	NR
Mauritania	2,484,000	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	5,738,400	NR
Nigeria	75,009,250	NR
Papua New Guinea	820,800	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	2,190,300	NR
Sierra Leone	4,248,000	NR
Solomon Islands	100,800	NR
South Africa	30,999,200	7,945,607
South Korea	3,411,000	1,516,527
South Sudan	5,862,650	NR
Sudan	17,312,300	NR
Swaziland	302,400	NR
Switzerland	200	NR
Syrian Arab Republic (Syria)	3,458,400	NR
Togo	2,620,800	NR
Trinidad and Tobago	259,200	NR
Tunisia	1,540,800	NR
Turkey	832,800	NR
Uganda	23,388,000	NR
Ukraine	1,202,400	NR
United Republic of Tanzania	34,890,150	NR

Table 8: Cumulative Subject Exposure to the Ad26.COV2.S Vaccine (Launch to 28 February 2023)

Region/Country/Territory	Number of Distributed Doses[a]	Number of Administered Doses[b,c]
Uzbekistan	1,003,150	NR
Vanuatu	43,150	NR
Yemen	1,197,600	NR
Zambia	12,367,050	NR
US	***41,225,650[e]***	***18,982,882***
Total	**611,193,650[f]**	**53,047,996**

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 the EEA countries/territories, from the KDCA for South Korea, from the Ministério da Saúde for Brazil, and from the NDH for South Africa. The data for administered doses for Brazil was last updated by the Ministério da Saúde website on 15 November 2021, and for Germany, the data for administered doses was last updated by the 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 28 February 2023.

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 611,193,650 doses of Ad26.COV2.S vaccine were distributed worldwide from launch to 28 February 2023.

A total of 53,047,996 doses of Ad26.COV2.S vaccine were administered worldwide from launch to 28 February 2023.

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 9.

Table 9: Total Number of Subjects With the Homologous Ad26.COV2.S Vaccine Booster Doses

Country/Territory	Interval	Cumulative
South Africa	133,775	1,520,478
South Korea[a]	8	27,032
US[b]	19,013	1,585,122
Total	**152,796**	**3,132,632**

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

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

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

A total of 152,796 subjects were administered the homologous Ad26.COV2.S vaccine booster dose in South Africa, South Korea, and the US from 01 September 2022 to 28 February 2023.[13]

A total of 3,132,632 subjects were administered the homologous Ad26.COV2.S vaccine booster dose in South Africa, South Korea, and the US from launch to 28 February 2023.[13]

Exposure by Age for Ad26.COV2.S in EEA

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

Post-authorisation use in special populations

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

5.3. Other Post-approval Use

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

6. DATA IN SUMMARY TABULATIONS

Database

The Company global safety database contains adverse event (AE) reports received from several sources: spontaneous notification, regulatory authorities, medical literature, clinical trials, post-marketing studies, registries, and other solicited sources.

The Cumulative Summary Tabulations of Serious Adverse Events From Clinical Trials (CT Tabulations) display all serious AEs from clinical trials. The CT Tabulations inclusion criteria was expanded: all clinical trials are in scope (including Company-sponsored and non-Company-sponsored clinical trials). However, protocols which do not report serious AEs are not displayed in the output.

The Cumulative and Interval Summary Tabulations From Post-marketing (PM) Sources inclusion criteria was expanded to include adverse reactions (ARs) from special situation cases (eg, pregnancy, overdose, medication error) with no additional ARs reported. No ARs from any type of studies (ie, clinical trials, non-interventional post-marketing studies and other solicited sources) are reported in the "Spontaneous" column of the PM tabulations.

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

Nonserious ARs from non-interventional post-marketing studies and other solicited sources are not presented in either of the tabulations.

Interval is defined as all cases received during the reporting period of this PBRER which have been reviewed and assessed. Within this PBRER, the term initial will be used to present all initial cases received. Cumulative is defined as all cases received (initial and follow-ups) from launch to the end date of this PBRER.

Please refer to Sections 6.2 and 6.3 for details regarding content of tabulations in appendices.

Primary Dose versus Booster Dose

Primary dose is defined as the first incidence of administration of the vaccine and booster dose is defined as administration of the vaccine after the primary dose. Although the overall tabulations contain all cases and events (primary dose and booster dose), the searches for each topic were conducted separately based on the configuration outputs. Within this PBRER, primary dose and booster dose subsections are presented separately for each topic. As such, the counts of each subsection are not additive.

6.1. Reference Information

All events are coded using Medical Dictionary for Regulatory Activities (MedDRA), version 25.1. 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 event(s) (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])[14] received cumulatively to the DLD of this PBRER. These ARs are derived from non-interventional post-marketing studies, other solicited sources and spontaneous notification, including reports from healthcare professionals, consumers, scientific literature, and regulatory authorities. Appendix 2.2 also displays ARs from special situation cases (eg, pregnancy, off-label use, overdose, medication error) with no additional ARs reported.

Data are presented side-by-side and organised by MedDRA SOC and then Preferred Terms (PTs) in international order. An AR received during the current reporting interval is captured in both the Interval and Cumulative columns. The count of ARs received during the interval period comprises all ARs (whether new or not) from both initial and follow-up individual case safety reports (ICSRs). The cumulative count would only increase for unique/new ARs from 1 reporting period to the next. The ARs displayed in the interval period tabulations are not additive to the previous cumulative figure(s).

During the reporting period, 7,626 serious ARs and 14,821 nonserious ARs were received from spontaneous sources, and 98 serious ARs were received from non-interventional post-marketing studies and other solicited sources.[15]

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

- General Disorders and Administration Site Conditions (7,439)
- Nervous System Disorders (3,529)
- Musculoskeletal and Connective Tissue Disorders (2,182)
- Infections and Infestations (1,680)
- Investigations (1,357)

Cumulatively, 99,521 serious ARs (98,343 spontaneous, 1,178 from non-interventional post-marketing studies and other solicited sources) were received by the Marketing Authorisation Holder (MAH).

[14] 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.

[15] This does not include interventional clinical trials.

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 DLP for this PBRER reporting period.

During the PBRER reporting period, 2 Company-sponsored interventional clinical trials (VAC31518COV1002 and VAC31518COV1003) of Ad26.COV2.S were completed. These clinical trials are briefly summarised below:

Trial VAC31518COV1002

This was a Phase 1, randomised, double-blind, placebo-controlled trial in healthy adults aged ≥20 to ≤55 years and ≥65 years in good health with or without stable underlying conditions in Japan to evaluate the safety, reactogenicity, and immunogenicity of Ad26.COV2.S at 2 dose levels, administered IM as 2-dose schedule.

Safety Summary

The safety data for Cohort 1 and Cohort 2 is described below.

Cohort 1:

Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

There were no deaths in Cohort 1. An SAE of sudden hearing loss (Grade 4) was reported in 1 participant from the 5×10^{10}, 5×10^{10} vp group during post-dose 1 follow-up. One participant from the 1×10^{11}, 1×10^{11} vp group experienced an AE of blood pressure increased (Grade 3) during post-dose 1 follow-up and resulted in study vaccine discontinuation. Both events resolved during their time on the study and were considered not related to the study vaccine by the investigator. No Adverse Event of Special Interest (AESI) and suspected AESI were reported.

Solicited Adverse Events

Vaccination site pain was the most frequently reported solicited local AE. The 3 most frequently reported solicited systemic AEs were fatigue, headache, and myalgia for both active vaccine groups.

The majority of the solicited AEs were of Grade 1 or 2 severity. The frequency of solicited AEs of ≥Grade 3 severity was lower post-dose 2 than post-dose 1, and it was lower in the 5×10^{10}, 5×10^{10} vp group compared with the 1×10^{11}, 1×10^{11} vp group, both post-dose 1 and post-dose 2.

A total of 3/50 (6.0%) participants in the 1×10^{11}, 1×10^{11} vp group reported Grade 4 solicited systemic AEs of pyrexia, post-dose 1. All events of Grade 4 pyrexia resolved in ≤4 days and were considered related to the study vaccine by the investigator.

Unsolicited Adverse Events

The majority of the unsolicited AEs were Grade 1 or 2 severity. No Grade 4 unsolicited AEs were reported. All Grade 3 unsolicited AEs were reported post-dose 1.

No participants experienced COVID-19 related AEs in Cohort 1. Overall, the percentages of participants with abnormal safety laboratory were very low and no notable differences were noted between vaccine and placebo groups and vaccine dose levels. The most frequent vital sign abnormalities were bradycardia and abnormal respiratory rate. The majority of reported abnormalities were Grade 1 severity. No unsolicited AEs related to vital signs were reported for Cohort 1.

Cohort 2

Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

One death was reported in Cohort 2. The cause of the death was acute myocardial infarction and was considered as not related to the study vaccine by the investigator. A total of 6 participants reported the following SAEs: schwannoma, embolic stroke, intervertebral disc protrusion, acute myocardial infarction, cystocele and uterine prolapse, and constipation (all SAEs reported at Grade 4). None of these SAEs were considered as related to the study vaccine by the investigator.

From the time of local approval of protocol Amendment 5 onwards (8 June 2021), Thrombosis with Thrombocytopenia Syndrome (TTS) was considered to be an AESI. Suspected AESIs (thrombotic events and/or thrombocytopenia [defined as platelet count below 15×10^4/μL]) were recorded from the moment of vaccination until the end of the trial/early withdrawal. An AESI Adjudication Committee with appropriate expertise was established to evaluate each suspected AESI and determine whether it is a case of TTS. Three participants reported the following suspected AESIs: embolic stroke (Grade 4), acute myocardial infarction (Grade 4), and thrombocytopenia (Grade 2). Embolic stroke and thrombocytopenia were not considered a case of TTS by the AESI adjudication committee. Only acute myocardial infarction event was assessed as a case of TTS by the committee, Brighton Collaboration level 3 (Brighton Collaboration 2021), CDC criteria "non Tier-1" (Shimabukuro 2021). None of these suspected AESIs were considered as related to the study vaccine by the investigator.

Solicited Adverse Events

Vaccination site pain was the most frequently reported solicited local AE. The 3 most frequently reported solicited systemic AEs were fatigue, headache, and myalgia for both active vaccine groups.

The majority of the solicited AEs were of Grade 1 or 2 severity. Grade 3 solicited systemic AEs were reported only post-dose 1 by 1 participant each in the 5×10^{10}, 5×10^{10} vp group and 1×10^{11}, 1×10^{11} vp group.

Unsolicited Adverse Events

The most frequently reported unsolicited AE was administration site pruritus, reported in 4/50 (8.0%), 1/49 (2.0%), and 2/26 (7.7%) in the 5×10^{10}, 5×10^{10} vp; 1×10^{11}, 1×10^{11} vp; and placebo, placebo groups, respectively. The majority of the unsolicited AEs were Grade 1 or Grade 2 severity. No unsolicited AEs of ≥Grade 3 severity considered related to the study vaccine were reported post-dose 1 or post-dose 2.

The majority of the unsolicited AEs were Grade 1 or 2 severity. A total of 2/50 (4.0%) participants in the 1×10^{11}, 1×10^{11} vp group reported a related unsolicited AE of Grade 3 severity post-dose 1. No unsolicited AEs of ≥Grade 3 severity considered related to the study vaccine were reported post-dose 2.

No participants experienced COVID-19 related AEs. Overall, the percentages of participants with abnormal safety laboratory values were very low with no notable differences noted between vaccine and placebo groups or vaccine dose levels. No laboratory abnormalities were reported as AEs. The most frequent vital sign abnormalities were bradycardia, abnormal respiratory rate, and hypertension (diastolic and systolic). The majority of reported abnormalities were Grade 1 severity. The vital abnormality of Grade 3 blood pressure increased was reported in 1 participant, post-dose 1.

Immunogenicity Summary

Neutralising antibodies to wt SARS-CoV-2 were measured in the wtVNA. Neutralising antibody titres increased from baseline to Day 366. At Day 29 robust neutralising antibody responses were seen in both Cohort 1 and Cohort 2, with responder rates ≥96% and geometric mean increase (GMIs) from baseline ≥3-fold. Responses further increased at Day 57 with responder rates ≥95%.

For Cohort 1, participants who received a second dose of Ad26.COV2.S at Day 57 (median=78 days) had a significant boost in humoral responses, with responses at Day 71 (14-day post-dose 2) representing GMIs from baseline of greater than 18- and 25-fold in the 5×10^{10}, 5×10^{10} vp group and 1×10^{11}, 1×10^{11} vp group, respectively.

For Cohort 2, participants who received a second dose of Ad26.COV2.S at Day 57 had a significant boost in humoral responses, with responses at Day 71 (14-day post-dose 2) representing GMIs from baseline of greater than 9- and 11-fold in the 5×10^{10}, 5×10^{10} vp group and 1×10^{11}, 1×10^{11} vp group, respectively.

Responses were durable, with a trend of only minimal decline for at least Day 85, following immunisation.

Durability of the neutralising antibody response: in younger adults (Cohort 1), a sustained increase in humoral responses from Day 29 up to 3 months post-vaccination was seen. Subsequently, between Day 85 and Day 366 (1-year post-dose, 1- and 10-months post-dose 2), neutralising antibody titres minimally declined below the Day 85 peak in both active vaccine groups in which responses remained stable between Day 239 and Day 366. Despite the decreases seen at Day 239 and Day 366, with responder rates ≥94%, and GMT ranged from 251 to 618 across the active vaccine groups. The responses at Day 239 and Day 366 represented GMIs from baseline of around 4.5-5.1 and 8.5-10.4-fold in the 5×10^{10}, 5×10^{10} vp and 1×10^{11}, 1×10^{11} vp groups, respectively. The responses at Day 239 and Day 366 in both active groups were similar to Day 29.

In older adults (Cohort 2), an increase in humoral responses from Day 29 up to 3 months post-vaccination was seen. Subsequent analysis between Day 85 and Day 366 (1-year post-dose 1 and 10 months post-dose 2), neutralising antibody titres declined below the Day 85 peak in both active vaccine groups in which responses remained stable between Day 239 and Day 366. Despite the decreases seen at Day 239 and Day 366, responses were ≥85%, and GMT ranged from 146 to 268 across the active vaccine groups. The responses at Day 239 and Day 366 represented GMIs from baseline of around 2.8 to 3.1 and 4.2 to 4.7-fold in the 5×10^{10}, 5×10^{10} vp and 1×10^{11}, 1×10^{11} vp groups, respectively. The responses at Day 239 and Day 366 in both active groups were slight lower than Day 29.

The use of antipyretics/analgesics post-dose 1 and post-dose 2 did not appear to have negative impact on the neutralising antibody response in both cohorts.

Overall, in conclusion, the 2-dose 5×10^{10} vp regimen had an acceptable safety and reactogenicity profile. Higher reactogenicity was observed with the 1×10^{11} vp dose level than the 5×10^{10} dose level; however, overall, across cohorts, the 2-dose 1×10^{11} vp regimen was generally well tolerated. No significant safety issues were identified in this trial. For both dose levels, there was lower reactogenicity post-dose 2 compared with post-dose 1. In general, a lower reactogenicity profile was observed for the older adults compared to the younger adults.

The immunogenicity analysis performed in this trial showed that a single dose of Ad26.COV2.S at both dose levels induced humoral immune responses which are detectable up to 1-year post-dose 1 in participants aged ≥20 to ≤55 years and ≥65 years old. Participants in both age groups who received a second dose of Ad26.COV2.S at Day 57 had a boost in humoral responses that were durable, with only minimal decline up to Day 85 following immunisation. The humoral response declined below the Day 85 peak in both active vaccine groups in which responses remained stable between Day 239 and Day 366. Despite the decreases, the response in both active groups in younger adults were similar to Day 29 and in both active groups in older adults were slight lower than Day 29.

These data are in line with safety and immunogenicity data reported for Trial VAC31518COV1001.

These data supported the continued development of Ad26.COV2.S regimens at a dose level of 5×10^{10} vp for the prevention of COVID-19.

Trial VAC31518COV1003

This was a Phase 1, randomised, observer-blind, parallel-group trial to compare the safety, reactogenicity, and immunogenicity of Ad26.COV2.S at a single-dose of 5×10^{10} vp in 2 different volumes (0.3 mL and 0.5 mL) in healthy adults aged ≥18 to ≤65 years.

Overall, in conclusion, no safety issues were identified in adult participants after receiving the Ad26.COV2.S vaccine at a single dose of 5×10^{10} vp in a test volume of 0.3 mL. The safety and reactogenicity profile were in line with that of the authorised 0.5 mL presentations. No fatal AEs, AESIs, or AEs leading to study discontinuation were reported. Serious AEs were reported for 1 participant in the 0.3-mL vaccination group and 1 participant in the 0.5-mL vaccination group during the follow-up phase. All SAEs were considered to be not related to the study vaccine by the investigator.

The immunogenicity analyses performed in this study showed that a single dose of Ad26.COV2.S at 5×10^{10} vp (in 0.3 mL or 0.5 mL) induces humoral responses which are durable up to at least 6 months post vaccination (last time point analysed), in adult participants.

7.2. Ongoing Clinical Trials

An "ongoing clinical trial" is defined as a trial for which the first informed consent form has been signed, but for which a final CSR is not available at the data-lock point for this PBRER reporting period, regardless of whether the last subject last visit has occurred.

During the PBRER reporting period, 9 Company-sponsored, interventional clinical trials (VAC31518COV1001, VAC31518COV2004, VAC31518COV2008, VAC31518COV3001, VAC31518COV3003, VAC31518COV3005, VAC31518COV3006, VAC31518COV3009, and VAC18193RSV2008) of Ad26.COV2.S were ongoing. Of these 9 clinical trials, 1 clinical trial (VAC18193RSV2008) was initiated during the PBRER reporting period. These clinical trials are briefly summarised below:

- **Trial VAC31518COV1001:** This is a Phase 1/2a, randomised, double-blind, placebo-controlled, first-in-human, multicentre trial in healthy adults aged ≥18 to ≤55 years and aged ≥65 years in good health with or without stable underlying conditions to evaluate the safety, reactogenicity, and immunogenicity of Ad26.COV2.S at 2-dose levels, administered IM as a single-dose or 2-dose schedule, with a single booster vaccination administered in 1 cohort. An ad hoc booster vaccination with Ad26.COV2.S will be provided in open-label fashion to eligible participants who have previously received 1 or more doses of any COVID-19 vaccine, if the last vaccination was ≥6 months ago.

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

- **Trial VAC31518COV2004:** This is a Phase 2, open-label, multicentre trial to evaluate the safety, reactogenicity, 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 period.

- **Trial VAC31518COV2008:** This is a Phase 2, randomised, double-blind, parallel, multicentre trial to evaluate the immunogenicity, reactogenicity, and safety of Ad26.COV2.S administered as a 1-dose booster vaccination (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).

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

- **Trial VAC31518COV3001:** This is a Phase 3, randomised, double-blind, placebo-controlled, multicentre, pivotal efficacy, and safety trial in adults ≥18 years of age. The efficacy, safety, and immunogenicity of Ad26.COV2.S is evaluated in participants living in, or going to, locations with high risk for acquisition of SARS-CoV-2 infection after administration of study vaccine. All participants who initially received placebo in the double-blind phase were offered a single dose of Ad26.COV2.S vaccine 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.

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

- **Trial VAC31518COV3003:** This is a Phase 3, randomised, double-blind trial to evaluate 6 dose levels of Ad26.COV2.S administered as a 2-dose schedule in healthy adults aged 18 to 55 years, inclusive. This trial consists of 2 parts: main trial and sub-trial. In the main trial, the safety, reactogenicity, and immunogenicity of 1 dose (dose 1 of the 2-dose regimen) and 2 doses of Ad26.COV2.S will be evaluated. In the sub-trial, additional adult participants aged 18 to 55 years will be enroled (into study groups 1, 3, 5, and 6) to further characterise the innate, pro-inflammatory, and other relevant (eg, pro-thrombotic) responses to Ad26.COV2.S to better understand a possible risk to TTS events.

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

- **Trial VAC31518COV3005:** This is a Phase 3, randomised, double-blind, parallel, multicentre trial 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.

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

- **Trial VAC31518COV3006:** This is a Phase 2, randomised, observer-blind, pivotal 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.

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

- **Trial VAC31518COV3009:** This is a Phase 3, randomised, double-blind, placebo-controlled, multicentre, pivotal efficacy and safety trial in adults ≥18 years of age. The efficacy, safety, and immunogenicity of Ad26.COV2.S is 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 and participants are in long-term follow-up for safety.

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

- **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 vaccine 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 period.

Independent Data Monitoring Committee/Data Safety Monitoring Board

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

7.3. Long-term Follow-up

During the reporting period, no long-term follow-up information for Ad26.COV2.S became available.

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 period.

7.5. New Safety Data Related to Fixed Combination Therapies

Ad26.COV2.S is currently not under development as a fixed-dose combination or multidrug regimen.

8. FINDINGS FROM NON-INTERVENTIONAL STUDIES

Based on review of the data from noninterventional study for Ad26.COV2.S during the PBRER reporting period, 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 (VAC31518COV4004 and VAC31518COV4019), collaborative, and publicly available RWE studies reporting on the vaccine effectiveness of Ad26.COV2.S are described below:

Study VAC31518COV4004

Interim results for the primary objective were available for Study VAC31518COV4004, multi-centre, multi-country, hospital-based case-control study with Test-Negative Control (TNCC) 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.

The interim results from Janssen's multi-country TNCC study (VAC31518COV4004) through July 2022 demonstrated that a single-dose of Ad26.COV2.S provided protection against laboratory confirmed SARS-CoV-2 SARI hospitalisations.

Study VAC31518COV4019

Interim results (with approximately 3 months and 6 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 Study VAC31518COV4019, 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], messenger Ribonucleic Acid (mRNA;1273 [2 doses]) using both open and closed-claims data elements aggregated by Health Verity.

The interim results from Janssen's large, longitudinal US cohort study (VAC31518COV4019) demonstrated that both homologous and heterologous booster vaccines provided protection against COVID-19 related hospitalisations for up to 6 months. There have been other RWE studies that have been recently published by researchers, that evaluate the vaccine effectiveness (VE) of single dose and booster Ad26.COV2.S vaccine. The protection against COVID-19 varies between different variants of concern (VOC)s. 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 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. These literatures confirm 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

During the PBRER reporting period, 8 interventional clinical trials sponsored by other organisations/institutions were ongoing: 1 interventional clinical trial (COV-BOOST [VAC31518COV2009]) sponsored by the University Hospital Southampton National Health

Services (NHS) Foundation Trust, 1 interventional clinical trial (VAC31518COV2012) sponsored by the Vaccine Trial Centre (Hospital for Tropical Diseases, Mahidol University, Thailand), 1 interventional clinical trial (VAC31518COV2016 [AUR1-8-341]) sponsored by The Aurum Institute NPC, 2 interventional clinical trials (VAC31518COV3012 [Sisonke {Together}] and VAC31518COV3021 [Sisonke Boost Open-Label Study {SISONKE2}]) sponsored by South African Medical Research Council (SAMRC), 1 interventional clinical trial (VAC31518COV3018) sponsored by the Mayo Clinic, 1 interventional clinical trial (VAC31518COV4012) sponsored by the National and Kapodistrian University of Athens, University Research Institute of Maternal and Child Health & Precision Medicine and 1 interventional clinical trial (DMID 21-0012) sponsored by National Institute of Health (NIH) were ongoing for Ad26.COV2.S. The summary and safety findings from these trials are presented below.

Trial COV-BOOST (VAC31518COV2009)

This is a Phase 2, randomised, multicentre trial conducting in the United Kingdom (UK) to determine reactogenicity and immunogenicity of booster vaccination against ancestral and novel variants of SARS-CoV-2. The trial will initially consist of several cohorts enroled in 2 or 3 stages.

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

During the reporting period, no significant safety information related to Ad26.COV2.S from this clinical trial became available.

Trial VAC31518COV2012

This is Phase 1/2, prospective, multicentre, observer-blind adaptive trial to assess the safety, reactogenicity, and immunogenicity of a booster dose of Ad26.COV2.S in adults ≥18 years of age in trial 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 DLP of this PBRER, 478 participants received Ad26.COV2.S in this trial.

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

Trial VAC31518COV2016 (AUR1-8-341)

This is a Phase 2a, randomised, observer-blind, multicentre trial of the safety and immunogenicity of COVID-19 vaccine strategies in Human Immunodeficiency Virus (HIV)-infected and HIV-uninfected adults. A total of 750 evaluable HIV-infected (660) and HIV-uninfected (90) adult participants meeting all entry criteria (all inclusion and no exclusion criteria) will be enroled in 3 treatment strategies in 3 participant groups dependent on prior vaccination with a single-dose of

Janssen (Group 1), 2 doses of Pfizer (Group 2), or no prior COVID-19 vaccination with evidence of prior SARS-CoV-2 infection (Group 3).

At the time of DLP of this PBRER, 231 participants received Ad26.COV2.S in this trial.

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

Trial VAC31518COV3012 (Sisonke [Together])

This is a Phase 3b, open-label, single-arm, multicentre, implementation trial to monitor the effectiveness of the single-dose of Ad26.COV2.S among Health Care Workers (HCW) at least 18 years of age as compared with the general unvaccinated population in South Africa. All HCWs who register on the National Vaccination Registry were eligible for enrolment.

At the time of DLP of this PBRER, 499,887 participants received Ad26.COV2.S in this trial.

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

Trial VAC31518COV3018

This is a Phase 3, prospective, open-label clinical trial with 1 randomised arm to evaluate the response of a heterologous additional dose with the Janssen Ad26.CoV2.S vaccine to provide vaccine induced immunity for immunocompromised kidney transplant patients after receiving 2 or more doses of the Pfizer or Moderna COVID-19 vaccine.

At the time of DLP of this PBRER, 35 participants received Ad26.COV2.S in this trial.

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

Trial VAC31518COV3021 (Sisonke Boost Open-label Study [SISONKE2])

This is a Phase 3b, open-label, single-arm, multicentre, implementation trial in Sisonke participants in South Africa at least 18 years of age. This trial will be conducted by Sisonke (VAC31518COV3012) sites in collaboration (where appropriate) with routine National Department of Health vaccination centres in South Africa. All Sisonke participants registered on the National Vaccination Registry were eligible for enrolment, if eligibility is met.

At the time of DLP of this PBRER, 250,878 participants received Ad26.COV2.S in this trial.

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

Trial VAC31518COV4012

This is a trial 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 the Ad26.COV2.S vaccine and boosting with either Ad26.COV2.S vaccine 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 vaccine and boosting with either Ad26.COV2.S vaccine or mRNA vaccines.

At the time of DLP of this PBRER, 298 participants received Ad26.COV2.S in this trial.

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

Trial DMID 21-0012

This is a Phase 1/2, open-label trial 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 trial is designed to assess the safety, reactogenicity, and immunogenicity of a delayed (>12 weeks) vaccine boost on a range of Emergency Use Authorisation-dosed COVID-19 vaccines (mRNA-1273 manufactured by ModernaTX, Inc.; BNT162b2 manufactured by Pfizer/BioNTech; or Ad26.COV2.S manufactured by Janssen Pharmaceuticals/Johnson & Johnson).

At the time of DLP of this PBRER, 150 participants received Ad26.COV2.S in this trial.

During the reporting period, no significant safety information related to Ad26.COV2.S from this clinical trial became available.

Overall, no significant safety findings from other clinical trials/studies were identified during the reporting period that had an impact on the benefit-risk balance of Ad26.COV2.S.

9.2. Medication Errors

Introduction

Cases of medication errors or potential medication errors are reviewed in all COVID-19 vaccine PBRERs. Medication error is synonymous with vaccination error.

Methods

The Company global safety database was searched for medically confirmed and medically unconfirmed cases, received during this reporting period, which coded to the Standardised MedDRA Query (SMQ) Medication errors (broad),[16] provided in Appendix 5.

Results/Discussion

During this reporting period, a total of 49 (44 medically confirmed and 5 medically unconfirmed) initial, primary dose cases reporting medication errors were retrieved. There were 6 serious and 43 nonserious cases which reported a total of 63 medication error events (5 serious, 58 nonserious).

During this reporting period, a total of 11 (3 medically confirmed and 8 medically unconfirmed) cases reported as booster were identified. There were 10 serious and 1 nonserious case, which reported a total of 11 medication error events (4 serious, 7 nonserious). All 11 cases were heterologous.

Post-marketing Sources (Including Spontaneous and Solicited) Cases

Primary Dose

During this reporting period, a total of 46 (41 medically confirmed and 5 medically unconfirmed) post-marketing, initial, primary dose cases reporting medication errors were retrieved. Of these 46 cases, 1 concerned a paediatric patient which is discussed in subsection 9.2.1, Paediatric Cases below. The remaining 45 cases reported 59 medication error events (3 serious, 56 nonserious) and are presented below.

Cumulatively, 2,505 (1,785 medically confirmed and 720 medically unconfirmed) post-marketing, primary dose cases reporting medication errors were retrieved. Of these 2,505 cases, 372 concerned paediatric patients which are discussed in subsection 9.2.1, Paediatric Cases below. The remaining 2,133 cases reported a total of 2,870 medication error events (35 serious; 2,835 nonserious) and are presented below.

An overview of these cases is presented in Table 10 below.

[16] 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.

Table 10: Characteristics of Selected Post-marketing Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Medication Errors

Case Characteristics		Number of Cases Received During the Interval Reporting Period=45	Number of Cases Received Cumulatively=2,133[a]
Sex	Male	16	713
	Female	12	685
	NR	17	735
Age (Years)[b]	18 to 35	7	321
Minimum: 19	36 to 50	5	302
Maximum: 80	51 to 64	6	351
Mean: 45.4	≥65	3	186
Median: 48	NR	24	926
Source	Spontaneous	44	2,121
	Clinical study (noninterventional, solicited)	1	11
Country/Territory	United States	38	1,833
	France	2	74
	Austria	1	4
	Canada	1	9
	Colombia	1	6
	Ireland	1	12
	South Africa	1	4
Event Characteristics		**Number of Events=59**	**Number of Events=2,870**
Seriousness (Event Level)[c]	Nonserious	56	2,835
	Serious	3	35
Outcome (Event Level)[c]	Not resolved	1	35
	Resolved	1	49
	NR	57	2,779

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 period (25 August 2022 to 24 February 2023).

b: The median and mean age calculation were based on the current reporting period (25 August 2022 to 24 February 2023).

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

Of these 45 post-marketing, primary dose cases received during the reporting period, the most frequently (n≥ 2) reported countries/territories of origin were the US (n=38) and France (n=2). These cases concerned 16 males, 12 females, and 17 did not report sex. The age range was from 19 to 80 years.

The frequency distribution of the MedDRA PTs of interest reported in cases (n=45) is presented in Table 11 below.

The majority of the cases included the MedDRA PTs Expired product administered, Poor quality product administered, and Product storage error, which 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 11: Frequency Distribution of MedDRA PTs in Post-marketing Primary Dose Cases Reporting Medication Errors With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
Expired product administered	0	26	4	539
Poor quality product administered	0	12	0	708
Product storage error	0	12	2	594
Product administered at inappropriate site	1	1	3	17
Device infusion issue	1	0	1	0
Inappropriate schedule of product administration	0	1	1	95
Interchange of vaccine products	1	0	2	7
Medication error	0	1	1	119
Product administration error	0	1	2	66
Product dispensing error	0	1	0	11
Product use issue	0	1	1	17

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

a: The MedDRA PTs of interest were sorted by decreasing order for the current reporting period (25 August 2022 to 24 February 2023). 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 period (25 August 2022 to 24 February 2023).

Of the 45 post-marketing, primary dose cases retrieved during the reporting period, none of the cases reported the PT Off label use.

The majority (82.2%; 37/45) of the cases involved medication errors without any additional AEs reported (classified as error without harm); whereas 17.8% (8/45) of cases reported medication errors with harm. These 8 cases reported 47 additional events (36 serious, 11 nonserious). The most frequently reported events of medication errors in these cases (n≥2) were expired product administered and product administered at inappropriate site (n=2 each).

The frequency distribution of additional AEs (n≥2) reported in 8 cases reporting medication errors with harm with the use of Ad26.COV2.S is presented in Table 12 below. Most of the serious AEs occurred in 2 patients who experienced rhabdomyolysis in association with either alcohol withdrawal syndrome or diabetic ketoacidosis caused by pump failure. Reported medication errors referred to interchange of vaccine products (second dose of unspecified vaccine at unspecified time after Ad26.COV2.S) and to device infusion issue, respectively.

Table 12: Frequency Distribution of Additional AEs in Post-marketing Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Medication Errors With Harm

Additional AEs	Number of Events Received During the Interval Reporting Period[a]		Number of Events Received Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
Anal incontinence	1	1	1	2
Confusional state	2	0	2	1
Pain	1	1	6	68
Rhabdomyolysis	2	0	2	0

Key: AE=Adverse Event

a: The AEs with a frequency ≥2 have been presented and sorted by decreasing order for the current reporting period (25 August 2022 to 24 February 2023). 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 period (25 August 2022 to 24 February 2023).

Booster Dose

During this reporting period, a total of 11 (3 medically confirmed and 8 medically unconfirmed) post-marketing, initial cases reported as booster were identified. None of these 11 cases concerned paediatric patients. These 11 booster dose cases reported 11 medication error events (4 serious, 7 nonserious) and are presented below.

Cumulatively, 1,079 (280 medically confirmed and 799 medically unconfirmed) post-marketing cases reported as booster were identified. Of these 1,079 cases, 7 concerned paediatric patients which are discussed in the subsection 9.2.1, Paediatric Cases below. The remaining 1,072 booster dose cases reported a total of 1,110 mediation error events (19 serious; 1,091 nonserious) and are presented below.

An overview of these cases is presented in Table 13 below.

Table 13: Characteristics of Selected Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Medication Errors

Case Characteristics		Number of Cases Received During the Interval Reporting Period=11	Number of Cases Received Cumulatively=1,072[a]
Sex	Male	6	503
	Female	5	525
Age (Years)[b]	18 to 35	1	214
Minimum: 26	36 to 50	2	267
Maximum: 83	51 to 64	2	182
Mean: 55.3	≥65	2	154
Median: 55	NR	4	245
Source	Spontaneous	8	748
	Clinical study (noninterventional, solicited)	2	313
	Clinical study (noninterventional,	1	11

Table 13: Characteristics of Selected Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Medication Errors

Case Characteristics		Number of Cases Received During the Interval Reporting Period=11	Number of Cases Received Cumulatively=1,072[a]
	unsolicited)		
Country/Territory	Germany	5	29
	United States	4	458
	Brazil	2	423
Classification	Heterologous	11	392
Event Characteristics		**Number of Events=11**	**Number of Events=1,110**
Seriousness (Event Level)[c]	Nonserious	7	1,091
	Serious	4	19
Outcome (Event Level)[c]	Resolved	1	7
	NR	10	1,095

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 period (25 August 2022 to 24 February 2023).
b: The median and mean age calculations were based on the current reporting period (25 August 2022 to 24 February 2023).
c: Seriousness and outcome have been presented for the EOI.

Of these 11 post-marketing cases reported as booster received during the reporting period, the reported countries/territories of origin were Germany (n=5), the US (n=4), and Brazil (n=2). These cases concerned 6 males and 5 females. The age range was from 26 to 83 years.

The frequency distribution of the MedDRA PTs of interest reported in cases reported as booster is presented in Table 14 below.

Table 14: Frequency Distribution of MedDRA PTs in Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Medication Errors

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
Interchange of vaccine products	4	4	16	12
Inappropriate schedule of product administration	0	3	0	879

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: The MedDRA PTs of interest are sorted by decreasing order for the current reporting period (25 August 2022 to 24 February 2023).
b: For the cumulative column, the events were presented in decreasing order based on the event counts of the current reporting period (25 August 2022 to 24 February 2023).

As displayed in Table 14, the most frequently reported MedDRA PTs of interest for this current reporting period was Interchange of vaccine products (n=8).

Of the 11 cases reported as booster, the majority (90.9%; 10/11) of them contained additional AEs (classified as medication errors with harm). These 10 cases reported 65 additional events (25 serious, 40 nonserious). The reported events of medication errors in these cases were interchange of vaccine products (n=8) and inappropriate schedule of product administration (n=2).

The frequency distribution of additional AEs (n≥2) reported in these 10 cases is presented in Table 15 below. Most of the frequently reported events were nonserious; and serious adverse events were reported in 10 patients, where the frequently reported adverse events were drug ineffective, gait inability and/or rheumatoid arthritis or COVID-19 infection.

Table 15: Frequency Distribution of Additional AEs in Post-marketing Cases Reported as Booster Involving Use of Ad26.COV2.S and Reporting Medication Errors With Harm

Additional AEs	Number of Events Received During the Interval Reporting Period[a]		Number of Events Received Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
Drug ineffective	3	0	8	0
COVID-19	1	1	7	22
Depression	0	2	0	3
Gait inability	1	1	1	5
Migraine	0	2	1	3
Palpitations	0	2	1	3
Rheumatoid arthritis	2	0	3	0
Suspected COVID-19	2	0	3	11

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

a: The AEs with a frequency ≥2 have been presented for the current reporting period (25 August 2022 to 24 February 2023). 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 period (25 August 2022 to 24 February 2023).

9.2.1. Paediatric Cases

Post-marketing Sources (Including Spontaneous and Solicited) Cases

Primary Dose

During this reporting period, a total of 1 medically confirmed (no medically unconfirmed) post-marketing, initial case reporting medication error in the paediatric population was retrieved. This spontaneous case concerned a 17-year-old male from [redacted] who experienced 1 nonserious event of product administered to patient of inappropriate age and an additional nonserious event of off label use, and hence the event of interest (EOI) did not represent a true medication error. No additional AEs were reported.

Cumulatively, 372 (194 medically confirmed and 178 medically unconfirmed) post-marketing, primary dose cases reporting medication errors in the paediatric population were retrieved. There were 23 serious and 349 nonserious cases which reported a total of 401 medication error events (7 serious, 394 nonserious).

Paediatric Booster Dose Cases

During this reporting period, 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 the paediatric population were identified. There were 1 serious and 6 nonserious cases which reported a total of 10 nonserious events of medication error.

Clinical Trial Cases

During this reporting period, a total of 3 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 period, 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 period, 1 primary dose with a reported medication error (incorrect vaccine administered without further information) and no booster cases were retrieved from a Janssen Supported Clinical Study.

Line Listings

Death: During the current reporting period (25 August 2022 to 24 February 2023), 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 dose 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 dose cases.

Conclusion

No new safety issues were identified through review of cases reporting medication errors including paediatric cases. Overall, no new patterns of cases reporting medication errors or potential medication errors were identified. The CCDS contains information for the provider on indication, proper administration, and storage of the vaccine.

10. NON-CLINICAL DATA

During the period covered by this report, the following nonclinical studies continue to be conducted with focus on TTS and results are pending (see Table 16).

Table 16: Overview of Ongoing Nonclinical Study With Focus on TTS for JNJ-78436735 (Ad26.COV2.S)

Nonclinical Study Number	Nonclinical Study Title
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; TTS=Thrombosis with Thrombocytopenia Syndrome

Further, the following nonclinical studies were completed during this reporting period and the results are summarised in below (see Table 17).

Table 17: Overview of Completed Nonclinical Studies with Focus on TTS for JNJ-78436735 (Ad26.COV2.S)

Nonclinical Study Number	Nonclinical Study Title	Nonclinical Data
TV-TEC-236300	Biophysical investigations on interactions between human platelet factor 4 and Ad26.COV2.S	A possible interaction between PF4 and Ad26.COV2.S that has been hypothesised to lead to induction of anti-PF4 antibodies has been assessed using 3 different biophysical techniques: DLS, BLI, and SPR. In DLS and BLI experiments, no direct interactions between PF4 and Ad26.COV2.S were observed. SPR data demonstrated that the induced binding of PF4 to Ad26.COV2.S as published by Baker et al. (Baker 2021)[a] is likely an experimental artefact. These findings are in line with findings of Michalik et al. (Michalik 2022)[b] using DLS, showing no complex formation of PF4 with Ad26.COV2.S. Therefore, it is unlikely that binding of Ad26-vector particles to PF4 is driving the pathology of TTS.
TOX15155	VAC31518 SARS-COV-2 vaccine (COVID-19): Immunogenicity and biodistribution/protein expression study in New Zealand white rabbits	Expression of S protein was assessed in the IM administration site, draining lymph nodes, and spleen by immunohistochemistry and in the blood by S-PLEX assay, on Days 1 and 11 following IM dosing in rabbits. A transient expression of the S protein was observed in the IM administration site, draining lymph nodes (iliac and/or popliteal), and blood on Day 1, with all tissues examined being negative for S protein expression on Day 11 post dosing. No adverse vaccine-related effects were noted. Overall, Ad26.COV2.S-induced S protein expression, including its bioavailability in blood, was not associated with a safety concern in this study, but does not allow S protein to be ruled out as a potential contributing factor in a multifactorial scenario of TTS induction following vaccination with Ad26.COV2.S in humans.

Key: Ad26.COV2.S=Adenovirus Type 26 Coronavirus 2 Spike; BLI=Biolayer Interferometry; DLS=Dynamic Light Scattering; IM=Intramuscular; PF4=Platelet Factor 4; SPR=Surface Plasmon Resonance; TTS=Thrombosis with Thrombocytopenia Syndrome

a: Baker AT, Boyd RJ, Sarkar D, et al. ChAdOx1 interacts with CAR and PF4 with implications for thrombosis with thrombocytopenia syndrome. Sci Adv. 2021; 7(49):(eabl8213).

Table 17: Overview of Completed Nonclinical Studies with Focus on TTS for JNJ-78436735 (Ad26.COV2.S)

Nonclinical Study Number	Nonclinical Study Title	Nonclinical Data

b: Michalik S, Siegerist F, Palankar E, et al. Comparative analysis of ChAdOx1 nCoV-19 and Ad26.COV2.S SARS CoV-2 vector vaccines. Haematologica. 2022;107(4):947-957.

The available (mechanistic) nonclinical data generated with Ad26.COV2.S do not allow to conclude on the potential mechanism of TTS. No new safety concerns were identified from nonclinical 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 (marketing authorisation holder). It should be noted that the literature searches are wider than those for individual case safety reports (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 and 16.3 of the PBRER for any new or significant safety findings that may impact safety topics. Unless additional safety information (apart from ICSR) is included, these literature references are not presented in this section of the PBRER.

In addition, if the Company becomes aware of new safety/efficacy information from unpublished abstracts/manuscripts these would also be considered for evaluation and the findings will be discussed.

Selected references and Sponsor Comments are presented below.

11.1. Product-Specific Literature

Gibson EA, Li H, Fruh V, et al. COVID-19 Vaccination and Menstrual Cycle Length in the Apple Women's Health Study. *MedRxiv.* 2023.

COVID-19 vaccination may be associated with change in menstrual cycle length following vaccination.

Methods: We conducted a longitudinal analysis within a subgroup of 14,915 participants in the Apple Women's Health Study (AWHS) who enrolled between November 2019 and December 2021 and met the following eligibility criteria: were living in the US, met minimum age requirements for consent, were English speaking, actively tracked their menstrual cycles, and responded to the COVID-19 Vaccine Update survey. In the main analysis, we included tracked cycles recorded when premenopausal participants were not pregnant, lactating, or using hormonal contraceptives. We used conditional linear regression and multivariable linear mixed-effects models with random intercepts to estimate the covariate-adjusted difference in mean cycle length, measured in days, between pre-vaccination cycles, cycles in which a vaccine was administered, and post-vaccination cycles within vaccinated participants, and between vaccinated and unvaccinated participants. We further compared associations between vaccination and menstrual cycle length by the timing of vaccine dose within a menstrual cycle (i.e., in follicular or luteal phase). We present Bonferroni-adjusted 95% confidence intervals (CI) to account for multiple comparisons.

Results: A total of 128,094 cycles (median=10 cycles per participant; interquartile range: 4 to 22) from 9,652 participants (8,486 vaccinated; 1,166 unvaccinated) were included. The average within-individual standard deviation in cycle length was 4.2 days. Fifty-five percent of vaccinated participants received Pfizer-BioNTech's mRNA vaccine, 37% received Moderna's mRNA vaccine, and 7% received the Johnson & Johnson/Janssen vaccine (J&J). We found no evidence of a difference between mean menstrual cycle length in the unvaccinated and vaccinated participants prior to vaccination (0.24 days, 95% CI: -0.34, 0.82). Among vaccinated participants, COVID-19 vaccination was associated with a small increase in mean cycle length (MCL) for cycles in which participants received the first dose (0.50 days, 95% CI: 0.22, 0.78) and cycles in which participants received the second dose (0.39 days, 95% CI: 0.11, 0.67) of mRNA vaccines compared with pre-vaccination cycles. Cycles in which the single dose of J&J was administered were, on average, 1.26 days longer (95% CI: 0.45, 2.07) than pre-vaccination cycles. Post-vaccination cycles returned to average pre-vaccination length. Estimates for pre vs post cycle lengths were 0.14 days (95% CI: -0.13, 0.40) in the first cycle following vaccination, 0.13 days (95% CI: -0.14, 0.40) in the second, -0.17 days (95% CI: -0.43, 0.10) in the third, and -0.25 days (95% CI: -0.52, 0.01) in the fourth cycle post-vaccination. Follicular phase vaccination was associated with an increase in MCL in cycles in which participants received the first dose (0.97 days, 95% CI: 0.53, 1.42) or the second dose (1.43 days, 95% CI: 1.06, 1.80) of mRNA vaccines or the J&J dose (2.27 days, 95% CI: 1.04, 3.50), compared with pre-vaccination cycles.

Conclusion: COVID-19 vaccination was associated with an immediate short-term increase in menstrual cycle length overall, which appeared to be driven by doses received in the follicular phase. However, the magnitude of this increase was small and diminished in each cycle following vaccination. No association with cycle length persisted over time. The magnitude of change associated with vaccination was well within the natural variability in the study population. Menstrual cycle change following COVID-19 vaccination appears small and temporary and should not discourage individuals from becoming vaccinated.

***Company Comments*:** The article presents, "*the relationship between COVID-19 vaccination and menstrual cycle length over time in the AWHS, a longitudinal digital cohort of people in the U.S. with manually tracked menstrual cycles". It "compare[s] pre-vaccination cycle lengths with those in which a vaccine dose was administered and cycles following vaccination*".

"*Cycles in which the single dose of J&J was administered were, on average, 1.26 days longer (95% CI: 0.45, 2.07) than pre-vaccination cycles. […] The conditional logistic regression model of the probability of a long cycle suggested that, compared with pre-vaccination cycles, participants were more likely to experience a long cycle during the cycle in which they received the J&J vaccine [OR = 2.17, 95% CI: 1.16, 4.04 (Table 2)]. […] For the J&J dose, follicular phase vaccination was associated with a 2.27 (95% CI: 1.04, 3.50) day increase in cycle length. There was*

no evidence of increased mean cycle length in cycles in which the first vaccine dose (0.21 days, 95% CI: −0.14, 0.57) or the J&J vaccine dose (0.39 days, 95% CI: −0.75, 1.53) were administered in the luteal phase".

According to the authors, "*Potential mechanisms underlying the change in menstrual cycle length may involve inflammation from the immune response to vaccination. This immune response may impact a) signalling between the hypothalamus, pituitary, and ovaries (HPO), resulting in i) prolongation of follicular recruitment and, as a result, elongation of menstrual cycle length,[...] or ii) suppression of the growth of the endometrial lining,[...] and b) endometrial stability in the luteal phase, causing a reduction in cycle length*".

Additional ad-hoc analysis on a menstrual disorder or post-menopausal haemorrhage following vaccination was conducted by the Company based on PRAC request in July 2021 including clinical data and published literature. Based on the literature review, "*there [was] insufficient information to warrant a change to the current RSI or risk minimization and mitigation measures regarding the occurrence of menstrual disorders or post-menopausal haemorrhage following administration of COVID-19 Vaccine Janssen*."

Based on the information available in the Signal Tracking System (STS), "*On 23 February 2022 a signal was identified for Menstrual cycle and uterine bleeding disorders and Postmenopausal haemorrhage with the use of COVID-19 VACCINE AD26.COV2.S based on an aggregate review of post marketing data reported in the Company database and the Food and Drug Administration Vaccine Adverse Event Reporting System database.*" The rationale for creating the signal was *"[...] the impact of the events on patient quality of life and the fact that is a safety topic with regulatory interest*." However, based on the review of data from the Global Safety database and the FDA Vaccine Adverse Event Reporting System (VAERS), Menstrual cycle and uterine bleeding disorders and Postmenopausal haemorrhage safety signal was not validated and was closed on 25 February 2022. Recently there is an ongoing signal identified in the STS in January 2023 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, that has been validated.

Although the study included "*a large sample size (120,815 menstrual cycles from 9,295 participants)*", considering limitations (is based on self-reported data, no laboratory data regarding hormone level measurements, selection biases) of the study, no safety signal was identified at this time.

Nguyen S, Bastien E, Chretien B, et al. Transverse Myelitis Following SARS-CoV-2 Vaccination: A Pharmacoepidemiological Study in the World Health Organization's database. *Ann Neurol.* 2022.

Transverse myelitis (TM) has recently been associated by health authorities with Ad26.COV2.S (Janssen/Johnson & Johnson), 1 of the 5 US FDA or European Medicines Agency (EMA) labeled SARS-CoV-2 vaccines. It is unknown whether a similar association exists for the other FDA or EMA labeled SARS-CoV-2 vaccines (BNT162b2 [Pfizer/BioNTech], mRNA-1273 [Moderna], ChAdOx1nCov-19 [Oxford-AstraZeneca], and NVX-CoV2373 [Novavax]). This study aimed to evaluate the association between SARS-CoV-2 vaccine class and TM.

Methods: This observational, cross-sectional, pharmacovigilance cohort study examined individual case safety reports from VigiBase, the World Health Organization's pharmacovigilance database. We first conducted a disproportionality analysis with the Information Component (IC) using the reports of TM that occurred within 28 days following exposure to FDA or EMA labeled SARS-CoV-2 vaccines, from 01 December 2020 (first adverse event related to a SARS-CoV-2 vaccine) to 27 March 2022. Secondly, we analysed the clinical features of SARS-CoV-2 vaccine-associated TM cases reported in VigiBase.

Results: TM was significantly associated both with the mRNA-based (n=364; IC 025 =0.62) and vector-based (n=136; IC 025 =0.52) SARS-CoV-2 vaccines that are authorised by the FDA or the EMA.

Conclusions: Findings from this observational, cross-sectional pharmacovigilance study showed that mRNA-based and vector-based FDA/EMA labeled SARS-CoV-2 vaccines may be associated with TM. However, because TM remains a rare event, with a previously reported rate of 0.28 cases per 1 million vaccine doses, the risk-benefit ratio in favour of vaccination against SARS-CoV-2 virus remains unchallenged. Rather, this study suggests that clinicians should consider the diagnosis of TM in patients presenting with early signs of spinal cord dysfunction after SARS-CoV-2 vaccination.

Company Comments:. "*[D]isproportionality analysis yielded significant associations between TM and both mRNA-based and vector-based SARS-CoV-2 vaccines (Table 1), with positive IC025 values of 0.62 and 0.52, respectively. Separately, the IC025 value was 0.69 for BNT162b2 (Pfizer/BioNTech), 0.16 for mRNA1273 (Moderna), 0.21 for ChAdOx1nCov-19 (Oxford–AstraZeneca) and 1.09 for Ad26.COV2.S (Janssen/Johnson & Johnson). […] For the 500 included TM cases, 280 (56%) were after vaccination with BNT162b2 (Pfizer/BioNTech), 84 (17%) after mRNA-1273 (Moderna), 95 (19%) after ChAdOx1nCov-19 (Oxford–AstraZeneca), and 41 (8%) after Ad26.COV2.S (Janssen/Johnson & Johnson) (Table 2).*"

TM is currently not listed in the CCDS v13 but is labeled in the EU SmPC. It has been and continues to be an AESI in the EU RMP version 4.2, so the topic is being reviewed, including WHO VigiBase data. This topic was presented in Section 16.3.6.4.7., Transverse Myelitis, in the PBRER covering the period 25 August 2021 through 24 February 2022. According to it, "*Cumulatively, 94 cases (65 medically confirmed and 29 medically unconfirmed) reporting transverse myelitis were identified. […] Based on the review of the literature (ie, Section 11), ongoing/completed clinical studies (ie, Sections 7, 8, and 9), relevant cases retrieved from the Company global safety database in the period and cumulatively, and an O/E analysis, no new critical safety information was identified during the reporting period for transverse myelitis. The Company will continue to closely monitor cases of transverse myelitis as an AESI.*" Currently in the STS there is an ongoing signal identified on 07 December 2022 for the event of "Transverse myelitis" with the use of COVID-19 vaccine AD26.COV2.S based on internal review following routine signal detection activities, that has been validated.

The current publication presents 41 cases after the Janssen vaccine from the WHO safety database, which does not provide enough evidence for determining causality association and does not add additional value to the above-mentioned cumulative assessment. No new safety information has been identified at this time.

Palassin P, Bres V, Hassan S, et al. Comprehensive Description of Adult-onset Still's Disease After COVID-19 Vaccination. *J Autoimmunity*. 2023;134.

Cases of adult-onset Still's disease (AOSD) have been reported after COVID-19 vaccination. Here we provide a comprehensive description and analysis of all cases of AOSD reported in the literature and in pharmacovigilance databases through April 2022. Disproportionality analyses of pharmacovigilance data were performed in order to further explore the association between vaccination and AOSD. We included 159 patients, 144 from the World Health Organization pharmacovigilance database and 15 from the literature. Detailed clinical characteristics were described for the cases from the literature and from the French pharmacovigilance database (n = 9). The cases of AOSD after COVID-19 vaccination concerned women in 52.2% of cases. The median age was 43.4 years. More than 80% of AOSD reports occurred during the first 3 weeks and concerned mostly the BNT162b2 mRNA vaccine. We identified 14.5% of disease flare with a median time-to-onset (TTO) of AOSD flare-up significantly shorter than for the new onset form. More than 90% patients received steroids. Although all cases were considered serious and required

hospitalisation, most cases presented a favourable outcome (67.1%) with a good response to corticosteroid therapy with a mean time to recovery of 7.2 days. Disproportionality analyses suggested that AOSD was associated with COVID-19 vaccines as well as other vaccines. AOSD was nearly 5 times more frequently reported with COVID-19 vaccines than with all other drugs. Clinicians should be informed about the potential risk of AOSD onset or flare following COVID vaccines and the importance of its early detection to optimize its management.

***Company Comments*:** No new safety information related to Ad26 platform. Disproportionality analyses were conducted to explore the association between vaccination and AOSD. Overall, the study included 159 patients: 144 from the WHO pharmacovigilance database and 15 from the literature for the period up to April 2022. Based on the study results, "*Disproportionality analyses suggested that AOSD was associated with COVID-19 vaccines as well as other vaccines. AOSD was nearly 5 times more frequently reported with COVID-19 vaccines than with all other drugs*." Out of 159 described cases, only 7 were reported after Janssen vaccine and 37 after AstraZeneca adenovirus-based vaccine. As stated by the authors, "*AOSD after vaccination occurred mostly after the first dose and generally during the first three weeks following vaccination. Interestingly, our study shows a significantly shorter time to onset for flares than for new onset forms*." In addition, the authors stated, "*Even if a definite causal link between AOSD and COVID-19 vaccination could not be asserted, our disproportionality analyses suggested that COVID-19 vaccines could increase the risk of AOSD*."

According to the latest PBRER covering the period 24 February 2022 to 24 August 2022, "*Acute aseptic arthritis [including Still's disease] is listed as an AESI in the cRMP, EU RMP, and the US PVP."[....] According to the MHA conclusion and PRAC feedback to the latest PBRER (24February 2022 to 24 August/2022)".* Based on the evaluation of the cases, and review of safety from other sources, the information is consistent with the information known about acute aseptic arthritis. The Company will continue to closely monitor acute aseptic arthritis as an AESI."

The reviewed study doesn't provide any safety concern given the known information about acute septic arthritis. Hence, no safety observation is identified at this time.

Patone M, Mei XW, Handunnetthi L, et al. Risk of Myocarditis After Sequential Doses of COVID-19 Vaccine and SARS-CoV-2 Infection by Age and Sex. *Circulation.* 2022. 146;10 (743-754)

Myocarditis is more common after severe acute respiratory syndrome coronavirus 2 infection than after COVID-19 vaccination, but the risks in younger people and after sequential vaccine doses are less certain.

Methods: A self-controlled case series study of people ages 13 years or older vaccinated for COVID-19 in England between 01 December 2020 and 15 December 2021, evaluated the association between vaccination and myocarditis, stratified by age and sex. The incidence rate ratio and excess number of hospital admissions or deaths from myocarditis per million people were estimated for the 1 to 28 days after sequential doses of adenovirus (ChAdOx1) or mRNA-based (BNT162b2, mRNA-1273) vaccines, or after a positive SARS-CoV-2 test.

Results: In 42,842,345 people receiving at least 1 dose of vaccine, 21,242,629 received 3 doses, and 5,934,153 had SARS-CoV-2 infection before or after vaccination. Myocarditis occurred in 2,861 (0.007%) people, with 617 events 1 to 28 days after vaccination. Risk of myocarditis was increased in the 1 to 28 days after a first dose of ChAdOx1 (incidence rate ratio, 1.33 [95% CI, 1.09 to 1.62]) and a first, second, and booster dose of BNT162b2 (1.52 [95% CI, 1.24 to 1.85]; 1.57 [95% CI, 1.28 to 1.92], and 1.72 [95% CI, 1.33 to 2.22], respectively) but was lower than the risks after a positive SARS-CoV-2 test before or after vaccination (11.14 [95% CI, 8.64 to 14.36] and 5.97 [95% CI, 4.54 to 7.87], respectively). The risk of myocarditis was higher 1 to 28 days after a second dose of mRNA-1273 (11.76 [95% CI, 7.25 to 19.08]) and persisted after a booster dose (2.64 [95% CI, 1.25 to

5.58]). Associations were stronger in men younger than 40 years for all vaccines. In men younger than 40-years-old, the number of excess myocarditis events per million people was higher after a second dose of mRNA-1273 than after a positive SARS-CoV-2 test (97 [95% CI, 91 to 99] versus 16 [95% CI, 12 to 18]). In women younger than 40 years, the number of excess events per million was similar after a second dose of mRNA-1273 and a positive test (7 [95% CI, 1 to 9] versus 8 [95% CI, 6 to 8]).

Conclusion: Overall, the risk of myocarditis is greater after SARS-CoV-2 infection than after COVID-19 vaccination and remains modest after sequential doses including a booster dose of BNT162b2 mRNA vaccine. However, the risk of myocarditis after vaccination is higher in younger men, particularly after a second dose of the mRNA-1273 vaccine.

***Company Comments*:** Authors used the UK "National Immunisation Database of COVID-19 vaccination to identify vaccine exposure" and linked it "*at the individual level, to national data for mortality (Office for National Statistics), hospital admissions (Hospital Episode Statistics and Secondary User's service data), and SARS-CoV-2 infection data (Second Generation Surveillance System)*" to calculate *"[i]ncidence rate ratios (IRR), the relative rate of hospital admissions or deaths caused by myocarditis in exposure risk periods relative to baseline periods, and their 95% CIs were estimated by the self-controlled case series model adjusted for calendar time*". Authors reported increased risk of myocarditis for AstraZeneca adenoviral vector COVID-19 vaccine within 1 to 28 days after 1st dose (1.33 [95% CI, 1.09 to 1.62]), however it was lower than the risks after a positive SARS-CoV-2 test before or after vaccination (11.14 [95% CI, 8.64 to 14.36] and 5.97 [95% CI, 4.54 to 7.87], respectively).

In the current Janssen COVID-19 vaccine CCDS myocarditis is not a listed event. On 19 July 2021, the signal was opened for myocarditis and pericarditis, and the signal was validated but not confirmed. As per PBRER covering the period from 25 August 2021 to 24 February 2022, "*On 17 October 2021, the Company received feedback from the US Center for Biologics Evaluation and Research (CBER) related to the Emergency Use Authorization (EUA) Amendment 27205 for use of a booster dose of the Janssen COVID-19 vaccine. Within said amendment, CBER proposed the addition of myocarditis and pericarditis to the US Fact Sheets for both Healthcare Practitioners and Recipients and Caregivers. In response to this request, the Company provided a cumulative review of Clinical Trial as well as Post-marketing data with Ad26.COV2.S. Based on the totality of the data, the Company concluded that the available data was insufficient to establish a causal association between Ad26.COV2.S and myocarditis/pericarditis.*". In the US PVP version 5 (internally approved 24 November 2021), myocarditis and pericarditis is listed as an important potential risk.

Considering the study design limitations and the lower bound value of the 95% CI no new safety information is detected at this time. Additional information on cardiac inflammatory disorders is found in Section 14, Late-Breaking Information

Sturkenboom M., Messina D., Paoletti O., de Burgos-Gonzalez et al. Cohort Monitoring of 29 Adverse Events of Special Interest Prior to And After COVID-19 Vaccination in Four Large European Electronic Healthcare Data Sources. *MedRxiv*. 2022.

This study aimed to monitor use of COVID-19 vaccines and incidence rates of pre-specified Adverse Event of Special Interest (AESI) of COVID-19 vaccines prior to and after COVID-19 vaccination. This study was not aimed to test a specific hypothesis.

Design: A retrospective cohort study including subjects from 01 January 2020 to 31 October 2021, or latest availability of data.

Setting: Primary and/or secondary health care data from four European (EU) countries: Italy, the Netherlands, the United Kingdom (UK), and Spain.

Participants: Individuals with complete data for the year preceding enrolment or those born at the start of observation time. The cohort comprised 25,720,158 subjects.

Interventions: First and second dose of Pfizer, AstraZeneca, Moderna, or Janssen COVID-19 vaccine.

Main outcome measures (29 AESI): Acute aseptic arthritis, Acute coronary artery disease, Acute disseminated encephalomyelitis (ADEM), Acute kidney injury, Acute liver injury, Acute respiratory distress syndrome, Anaphylaxis, Anosmia or Ageusia, Arrhythmia, Bells' palsy, Chilblain-like lesions death, Erythema multiforme, Guillain Barré Syndrome (GBS), Generalised convulsion, Haemorrhagic stroke, Heart failure, Ischemic stroke, Meningoencephalitis, Microangiopathy, Multisystem inflammatory syndrome, Myo/pericarditis, Myocarditis, Narcolepsy, Single organ cutaneous vasculitis (SOCV), Stress cardiomyopathy, Thrombocytopenia, Thrombotic thrombocytopenia syndrome (TTS), and Venous thromboembolism (VTE).

Results: 12,117,458 individuals received at least a first dose of COVID-19 vaccine: 54% with Comirnaty (Pfizer), 6% Spikevax (Moderna), 38% Vaxzevria (AstraZeneca) and 2% Janssen COVID-19 vaccine. AESI were very rare <10/100,000 PY in 2020, only thrombotic and cardiac events were uncommon. After adjustment for factors associated with severe COVID, 10 statistically significant associations of pooled incidence rate ratios remained based on dose 1 and 2 combined. These comprised anaphylaxis after AstraZeneca vaccine, TTS after both AstraZeneca and Janssen vaccine, erythema multiforme after Moderna, GBS after Janssen vaccine, SOCV after Janssen vaccine, thrombocytopenia after Janssen and Moderna vaccine and VTE after Moderna and Pfizer vaccines. The pooled rate ratio was more than two-fold increased only for TTS, SOCV, and thrombocytopenia.

Conclusion: We showed associations with several AESI, which remained after adjustment for factors that determined vaccine roll out. Hypotheses testing studies are required to establish causality.

***Company Comments*:** This preprint article presents a retrospective cohort study, which aimed "*to monitor and estimate the incidence rates of AESI in vaccinated and non-vaccinated persons by data source over the period 01 January 2020 to 31 October 2021 by brand and dose of vaccine and to compare the incidence rates of AESI in the window 28 days after vaccination with dose 1 or dose 2 with the incidence rates of AESI of non-vaccinated people in 2020. Overall, 12,117,458 individuals were monitored who received at least a first dose of COVID-19 vaccine: 54% with Comirnaty (Pfizer), 6% Spikevax (Moderna), 38% Vaxzevria (AstraZeneca), and 2% Janssen COVID-19 vaccine*." *The authors stated that, "After adjustment for the factors associated with vaccination exposure using a Poisson regression, ten pooled (random effects) associations remained for dose (1 and 2) 28-day risk intervals combined, these included […] GBS after Janssen dose 1 (IRR=5.7, 95%CI: 1.4-23), SOCV after Janssen dose 1 (IRR=4.4, 95%CI 1.1-17.7), thrombocytopenia after Janssen dose 1 (IRR=2.3, 95%CI 1.3-4.1), […] TTS after […] Janssen dose 1 (IR=90,10-infinity)*". Based on the authors conclusion, "*[The study] showed associations with several AESI, which remained after adjustment for factors that determined vaccine roll out. Hypotheses testing studies are required to establish causality.*"

GBS, TTS, and immune thrombocytopenia (ITP) are listed adverse drug reactions (ADR) for Janssen vaccine in the CCDS. However, for cutaneous vasculitis there is an ongoing signal in STS. It is labeled in the EU Summary of Product Characteristics (SmPC) but not listed in the Janssen CCDS. According to the Pharmacovigilance Risk Assessment Committee (PRAC) feedback in the latest PBRER covering the period of 24 February 2022 to 24 August 2022, "*On 31 August 2022, both thrombocytopenia and SOVC were identified to have an association with Ad26.COV2.S from the review of the VAC4EU COVID vaccine safety monitoring system. Both events are already listed as adverse reactions following earlier assessments from the European Medicines Agency PRAC as immune thrombocytopenia and cutaneous small vessel vasculitis respectively. After the data lock point, the Company opened a safety signal based on the disproportionate reporting of vasculitis, particularly*

cutaneous vasculitis. The evaluation of this signal is ongoing and will be presented in the next PBRER."

11.2. Class Effect Literature

Beltrami-Moreira M, Bussel JB. A Narrative Review of Anti-SARS-COV-2 Vaccines and Immune Thrombocytopenia: Be Aware, But Reassured. *Clin Adv Hematol. Oncol.* 2022;20(9):572-578.

The COVID-19 pandemic gave rise to rapid development of anti-SARS-COV-2 vaccines using established and new technologies. Immune thrombocytopenia (ITP) is a bleeding disorder that has been associated with COVID-19 vaccine products that are currently in use. We reviewed the available evidence regarding the most commonly used vaccines against SARS-COV-2 in North America and Europe and their association with ITP. We found that population-based studies suggested a small increase in the incidence of ITP in persons receiving the ChAdOx1 nCoV-19 vaccine from Oxford-AstraZeneca, on the order of 6 cases per million doses administered. Severe bleeding was an even rarer event. Both mRNA-based and adenovirus-based vaccines have been associated with exacerbation of preexisting ITP in 6% to 20% of patients. ITP exacerbation is readily treatable with standard approaches when needed. Severe bleeding events are rare both in the general population and in persons with preexisting ITP, and overall, the benefits of vaccination outweigh the risks. Further identification of persons at the highest risk for complications (including those with ITP, VITT, and myocarditis) and clear communication of both risks and benefits of immunisation will continue to be paramount in the global campaign against COVID-19.

Company Comments: *This review article commented on the risk of ITP following immunisation with COVID-19 vaccines. Overall, the authors indicate available data suggests a small increase in cases of ITP in subject receiving ChAdOx1 (a vector-based vaccine) compared to mRNA vaccines. However, both mRNA and adenovector vaccines have been associated with an exacerbation of pre-existing ITP. Severe bleeding was very rare.*

ITP is considered an Important Potential Risk in the cRMP and US PVP, and as an Important Identified Risk (IIR) in the EU RMP (as 'Thrombocytopenia, including ITP'). A warning text also exists in the CCDS and EU Summary of Product Characteristics (SmPC) on the risk of bleeding in patients with a history of ITP. No new safety concern is identified form review of this data.

Borghi MO, Bombaci M, Bodio C, et al. Anti-phospholipid Antibodies And Coronavirus Disease 2019: Vaccination Does Not Trigger Early Autoantibody Production in Healthcare Workers. *Front. Immunol.* 2022;13: 930074.

A molecular mimicry between SARS-COV-2 and human proteins supports the possibility that autoimmunity takes place during COVID-19 contributing to tissue damage. For example, anti-phospholipid antibodies (aPL) have been reported in COVID-19 as a result of such mimicry and thought to contribute to the immunothrombosis characteristic of the disease. Consistently, active immunisation with the virus spike protein may elicit the production of cross-reactive autoantibodies, including aPL. We prospectively looked at the aPL production in HCW vaccinated with RNA- (BNT162b2, n. 100) or adenovirus-based vaccines (ChAdOx1, n. 50). Anti-cardiolipin, anti-beta2 glycoprotein I, anti-phosphatidylserine/prothrombin immunoglobulin G (IgG), IgA, and IgM before and after vaccination were investigated. Anti-platelet factor 4 immunoglobulins were also investigated as autoantibodies associated with COVID-19 vaccination. Additional organ (anti-thyroid) and non-organ (anti-nuclear) autoantibodies and IgG against human proteome were tested as further post-vaccination autoimmunity markers. The antibodies were tested 1 or 3 months after the first injection of ChAdOx1 and BNT162b2, respectively; a 12-month clinical follow-up was also performed. Vaccination occasionally induced low titres of aPL and other autoantibodies but did not affect the titre of pre-existing autoantibodies. No significant reactivities against a microarray of

approximately 20,000 human proteins were found in a subgroup of ChAdOx1-vaccinees. Consistently, we did not record any clinical manifestation theoretically associated with an underlying autoimmune disorder. The data obtained after the vaccination (2 doses for the RNA-based and 1 dose for the adenovirus-based vaccines), and the clinical follow-up are not supporting the occurrence of an early autoimmune response in this cohort of healthcare workers.

Company Comments: *The authors in the article explored the hypothetical production of aPL following COVID-19 vaccination as possible contributors for the onset of thrombosis in COVID-19 vaccine recipients. The authors also measured other autoimmune markers such as PF4, anti-cardiolipin, anti-beta2 glycoprotein I, anti-phosphatidylserine/prothrombin IgG, IgA, and IgM. Overall, the authors did not find evidence supporting the occurrence of an early autoimmune response.*

TTS is considered an IIR following vaccination with Ad26.COV2.S. Cerebrovascular events are listed as an AESI in the cRMP, EURMP, and US PVP. The mechanism behind TTS is not yet fully understood. No safety concern is identified based on the results from this study.

Garabet L, Eriksson A, Tjonnfjord E, et al. No Increase in Thrombin Generation or D-Dimer Levels After Anti-SARS-COV-2 Vaccines Including in Those With Anti-Platelet Factor 4 Antibodies. *Hemasphere.* 2022;6(Supplement 3):2956-2957.

Anti-SARS-COV-2 adenoviral-vectored-DNA vaccines have been linked to a rare but serious thrombotic post-vaccine complication called the VITT. VITT has raised concerns regarding the possibilities of increased thrombotic risk and thrombocytopenia after anti-COVID-19 vaccines.

Aim: To investigate whether anti-SARS-COV-2 vaccines can cause thrombocytopenia, coagulation activation and increased thrombin generation leading to a hypercoagulable state.

Methods: In this study, 567 healthcare personnel were included from 2 hospitals in Norway after obtaining informed consent. Of these, 521 were recruited 11 to 57 days post-vaccination with the first dose of ChAdOx1-S (Vaxzevria, AstraZeneca, UK) vaccine, and 46 were recruited prospectively prior vaccination with an mRNA vaccine, either elasomeran (Spikevax, Moderna, n=38) or tozinameran (Comirnaty, Pfizer-BioNTech, n=8). In the latter group, samples were acquired before and 1 to 2 weeks after vaccination. In addition to pre-vaccination samples, 56 unvaccinated healthy blood donors were recruited as controls (total n=102). Thrombin generation and D-dimer were analysed.

Results: None of the participants developed thrombosis/VITT; 12% reported cutaneous bleeding after vaccination; however, none had thrombocytopenia with platelet count $<100.10^9$/L. There were no significant differences in D-dimer or the parameters of thrombin generation between the 2 vaccine groups and the controls. Anti-PF4/polyanion antibodies (optical density >=0.4) were found in 11 of 513 individuals vaccinated with ChAdOx1-S vaccine (2.1%). None of the controls had anti-PF4/polyanion antibodies. Thrombin generation and D-dimer were not found to be higher in the ChAdOx1-S vaccinated individuals with anti-PF4 antibodies than in those without anti- PF4/polyanion antibodies. No differences in thrombin generation between the ChAdOx1-S group and the mRNA group. The median D-dimer level was slightly higher in the ChAdOx1-S group than the mRNA group, but both were within the normal range. Thrombin generation and D-dimer showed no changes after mRNA vaccination compared with baseline.

Conclusion: Anti-COVID-19 vaccines, both ChAdOx1-S and mRNA vaccines, did not lead to an increase in thrombin generation or D-dimer compared with controls, not even in the ChAdOx1-S vaccinated individuals with anti- PF4/polyanion antibodies. No differences were found between ChAdOx1-S and mRNA vaccines, and no increase in thrombin generation or D-dimer was found after mRNA vaccines compared with baseline levels. Our results are reassuring in the sense that no subclinical activation in the coagulation system was observed with these vaccines.

Company Comments: *The authors in the article explored the increase in thrombin or D-dimer levels in healthy HCWs vaccinated with either mRNA or adenovector (ChAdOx1) COVID-19 vaccine compared to unvaccinated controls. No increase in thrombin generation or D-dimer was observed compared with controls for either adenovector nor mRNA vaccines. The results were reassuring, as no subclinical activation in the coagulation system was observed.*

Venous Thrombotic events as well as Thrombocytopenia (including ITP) remain IIRs for Ad26.COV2.S. No safety concern is identified based on the results from this study.

Magdy R, Khedr D, Yacoub O, Attia A, Abdelrahman MA, Mekkawy D. Epidemiological Aspects of Headache After Different Types of COVID-19 Vaccines: An Online Survey. *Headache*. 2022;62(8):1046-1052.

COVID-19 vaccine-related side effects are a key concern with the emergence of various types of vaccines in the market. We aimed to assess the frequency and characteristics of headache following different types of COVID-19 vaccines.

Methods: Fully vaccinated people were recruited by a convenience sample through an online survey from 01 September 2021 to 01 December 2021. Detailed analysis of headache following vaccination was investigated. Participants with a history of pre-existing headaches were telephone interviewed by a neurologist to ascertain the type of headache.

Results: A total of 1,372 participants participated (mean age 32.9 +/- 11.1). The highest frequency of headache was reported with the adenoviral vector type (302/563, 53.6%), followed by mRNA vaccines (129/269, 48%) and then the inactivated type (188/540, 34.8%). Recipients of the adenoviral vector type had a significantly longer latency between vaccination and the headache onset (median 8 hours [5:12]) than recipients of the inactivated type (median 4 hours [2:8], $p < 0.001$). Headache intensity was significantly higher with the adenoviral vector type (median 6 [5:8]) than with the inactivated type (median 5 [4:7], $p < 0.001$). Adenoviral vector vaccines would increase the likelihood of headache by 2.38 times more than inactivated vaccines (odds ratio [OR] 2.38, 95% confidence interval [CI] 1.83 to 3.04, $p < 0.001$). Female sex and thyroid disease were significantly associated with headache related to COVID-19 vaccines (OR 1.52, 95% CI 1.16 to 1.99; OR 3.97, 95% CI 1.55 to 10.2, respectively).

Conclusion: Recipients of the COVID-19 vaccine should be counseled that they may experience headaches, especially after the adenoviral vector type. However, the intensity of such headache is mild to moderate and can resolve within a few days. Based on the current study design and the potential recall bias, these results may not be generalisable and should be preliminary.

Company Comments: *This comparative observational study showed a higher frequency of headache compared to mRNA vaccines and higher severity compared to inactivated vaccines. Overall, however, these episodes were mild and transient in nature.*

Headache is a very common ADR following Ad26.COV2.S, generally as a result of vaccine reactogenicity. The findings from this study are consistent with the known reactogenicity profile of Ad26.COV2.S from clinical trial experience. No safety concern is identified.

Stefanou MI, Palaiodimou L, Aguiar de Sousa D, et al. Acute Arterial Ischemic Stroke Following COVID-19 Vaccination: A Systematic Review And Meta-analysis. *Neurol.* 2022; 99(14):e1465-e1474.

Acute arterial-ischemic-stroke (AIS) has been reported as a rare AE following COVID-19 vaccination with mRNA or viral vector vaccines. However, data are sparse regarding the risk of post-vaccination AIS and its potential association with TTS.

Methods: A systematic review and meta-analysis of randomised-controlled clinical trials (RCTs), pharmacovigilance registries, registry-based studies, observational cohorts and case-series was performed with the aim to calculate: (1) the pooled proportion of patients presenting with AIS following COVID-19 vaccination; (2) the prevalence of AIS after mRNA and vector-based vaccination; (3) the proportion of TTS among post-vaccination AIS-cases. Patient characteristics were assessed as secondary outcomes.

Results: Two RCTs, 3 cohort, and 11 registry-based studies comprising 17,481 AIS-cases among 782,989,363 COVID-19 vaccinations were included in the meta-analysis. The pooled proportion of AIS following exposure to any COVID-19 vaccine type was 4.7 cases per 100,000 vaccinations (95% CI:2.2 to 8.1; I^2=99.9%). The pooled proportion of AIS following mRNA-vaccination (9.2 cases per 100,000 vaccinations; 95% CI: 2.5-19.3; I^2=99.9%) did not differ compared to adenovirus-based-vaccination (2.9 cases per 100,000 vaccinations; 95% CI: 0.3 to 7.8; I^2=99.9%). No differences regarding demographics were disclosed between patients with AIS following mRNA- or vector-based vaccination. The pooled proportion of TTS among post-vaccination AIS-cases was 3.1% (95%CI: 0.7 to 7.2%; I^2=78.8%).

Conclusions: The pooled proportion of AIS following COVID-19 vaccination is comparable to the prevalence of AIS in the general population and much lower than the AIS prevalence among SARS-COV-2-infected patients. TTS is very uncommonly reported in patients with AIS following COVID-19 vaccination.

Company Comments: *The article presents a systematic review and meta-analysis of cases of AIS following COVID-19 vaccination. In particular, the authors explored the differences in the frequency of AIS between mRNA and vector-based COVID-19 vaccines. Overall, the pooled proportion of AIS did not differ between vaccine types. TTS was rarely reported among AIS cases.*

TTS is considered an Important Identified Risk following vaccination with Ad26.COV2.S. Cerebrovascular events are listed as an AESI in the cRMP, EU RMP, and US PVP. No safety concern is identified based on the results from this study.

Wang JJ, Armour B, Chataway T, et al. Vaccine-induced Immune Thrombotic Thrombocytopenia (VITT) is Mediated by a Stereotyped Clonotypic Antibody. *MedRxiv*. 2022.

Vaccine-induced immune thrombotic thrombocytopenia (VITT) is a rare thromboembolic complication of adenoviral-vectored severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) vaccines, mediated by antibodies directed against platelet factor 4 (PF4). Given their causal role in VITT, identification of the molecular composition of anti-PF4 antibodies is crucial for developing better diagnostics and treatments. Here, we utilised a novel proteomic workflow to analyse the immunoglobulin variable (IgV) region composition of anti-PF4 antibodies at the level of the secreted proteome. Serum anti-PF4 IgG antibodies from 5 patients with VITT triggered by ChAdOx1 nCoV-19 vaccination were affinity purified by PF4-coupled magnetic beads and sequenced by mass spectrometry. We revealed a single IgG heavy (H)-chain species paired with a single lambda light (L)-chain species in all 5 unrelated patients. Remarkably, all L-chains were encoded by the identical IGLV3-21*02 gene subfamily with identical L-chain third complementarity determining region (LCDR3) lengths. Moreover, striking stereotypic features were also identified in heavy-chains anti-PF4 antibodies characterised by identical HCDR3 length and homologous sequences. In summary, we unraveled the molecular signature of highly stereotyped clonotypic anti-PF4 antibodies, indicating shared pathways of antibody production in VITT patients. These discoveries are critical to understand the molecular basis of this serious condition and develop novel therapies aimed at removing pathogenic clones.

Company Comments: *This proteomic analysis showed a highly stereotyped clonotypic anti-PF4 antibodies among 5 unrelated patients who developed VITT following vaccination with ChAdOx1, indicating shared pathways of antibody production in VITT patients.*

The mechanism for TTS (VITT) following vaccination with AD26.COV2.S remains unknown. No safety concern was identified from this study. The Company will continue to study the possible mechanistic pathways for TTS following vaccination.

Xie J, Prats-Uribe A, Gordillo-Maranon M, Strauss VY, Gill D, Prieto-Alhambra D. Genetic Risk and Incident Venous Thromboembolism in Middle-aged and Older Adults Following COVID-19 Vaccination. *J Thromb Haemost.* 2022;20(12):2887-2895.

COVID-19 vaccination has been associated with increased venous thromboembolism (VTE) risk. However, it is unknown whether genetic predisposition to VTE is associated with an increased risk of thrombosis following vaccination.

Methods: Using data from the UK Biobank, which contains in-depth genotyping and linked vaccination and health outcomes information, we generated a polygenic risk score (PRS) using 299 genetic variants. We prospectively assessed associations between PRS and incident VTE immediately after first- and the second-dose vaccination and among historical unvaccinated cohorts during the pre- and early pandemic. We estimated hazard ratios (HR) for PRS-VTE associations using Cox models.

Results: Of 359,310 individuals receiving 1 dose of a COVID-19 vaccine, 160,327 (44.6%) were males, and the mean age at the vaccination date was 69.05 (standard deviation [SD] 8.04) years. After 28- and 90-days follow-up, 88 and 299 individuals developed VTE, respectively, equivalent to an incidence rate of 0.88 (95% [CI] 0.70-1.08) and 0.92 (0.82-1.04) per 100,000 person-days. The PRS was significantly associated with a higher risk of VTE (HR per 1 SD increase in PRS, 1.41 (1.15 to 1.73) in 28 days and 1.36 (1.22 to 1.52) in 90 days). Similar associations were found in the historical unvaccinated cohorts.

Conclusions: The strength of genetic susceptibility with post-COVID-19-vaccination VTE is similar to that seen in historical data. Additionally, the observed PRS-VTE associations were equivalent for adenovirus- and mRNA-based vaccines. These findings suggest that, at the population level, the VTE that occurred after the COVID-19 vaccination has a similar genetic aetiology to the conventional VTE.

Company Comments: *The authors conducted a prospective cohort study to assess a self-generated PRS and the risk of VTE. The PRS was significantly associated with a higher risk of VTE (HR per 1 SD increase in PRS, 1.41 [1.15 to 1.73] in 28 days and 1.36 [1.22 to 1.52] in 90 days). In addition, the observed PRS VTE associations were equivalent for adenovirus- and mRNA-based vaccines.*

VTE is listed as an IIR for Ad26.COV2.S in the RMP. The findings from this study suggest the risk of VTE following vaccination may be linked to genetic predispositions.

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 VOC/variants of interest (VOI)s, there was a trend towards a decreased protection against moderate to severe/critical COVID-19 over time. Protection against moderate to severe/critical COVID-19 varied by (newly) emerging SARS-CoV-2 variants, including VOCs/VOIs, throughout the trial, and this potentially contributes to the observed decrease, although waning protection of Ad26.COV2.S cannot be excluded. Efficacy results from the primary analysis of ongoing Phase 3 trial VAC31518COV3009, in which an Ad26.COV2.S booster dose was administered 2 months after the first vaccination, suggest that protection against moderate to severe/critical COVID-19 (including against SARS-CoV-2 VOC) and severe/critical COVID-19 increased after a homologous booster dose administered 2 months after the single-dose primary vaccination.

When considering the VE against SARS-CoV-2 variants, including VOCs/VOIs, observed in Trial VAC31518COV3001, caution is needed when interpreting data where there were (too) few COVID-19 cases and/or confidence interval (CI)s were wide. Differences were observed in protection against moderate to severe/critical COVID-19. No reduction in VE estimates compared to that of the reference strain (VE estimate [95% CI]: 58.2% [34.96; 73.72] at least 28 days after vaccination) for the Alpha VOC and other variants was observed, while the VE estimates for the Delta, Gamma VOCs, Mu, Lambda VOIs were reduced (<36%). The VE estimate (95% CI) for the Beta VOC, at least 28 days after vaccination was 51.9% (19.06; 72.19). For severe/critical COVID-19, the VE estimates were 63% to 91% across variants with sufficient COVID-19 cases, such as Beta, Gamma VOCs, and Lambda, Mu VOIs. In summary, in the double-blind randomised placebo-controlled trial, a single-dose of Ad26.COV2.S provided at least 6 months of protection against severe/critical disease, hospitalisation, and death, with varying degrees of protection against symptomatic disease depending on the variant.

Since the clinical trial VE estimates are below 100%, particularly for mild and moderate disease, breakthrough cases in vaccinated individuals are expected to occur.

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

Overall, there is no safety concern related to lack of efficacy.

14. LATE-BREAKING INFORMATION

Update to US Emergency Use Authorisation Fact Sheet

On 13 March 2023, the US Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers) was updated to include a new Warning and Precautions statement for myocarditis and pericarditis. This update was a follow-up of the US FDA request on 14 February 2023 to update the US Emergency Use Authorisation (EUA) Fact Sheets with a warning statement as described in Section 3, Actions Taken in the Reporting Interval for Safety

Reasons (see Table 3). Similarly, the Fact Sheet for Recipients and Caregivers was updated to include these risks for myocarditis and pericarditis.

Of note, the 13 March 2023 updated Healthcare Providers Fact Sheets also included the final agreement to update the adverse reactions section for 'facial paralysis (including Bell's palsy)' with the updated Recipient and Caregivers Fact Sheet including 'weakness or paralysis of the muscles of the face'. The update for facial paralysis was in follow-up to the 15 July 2022 communication where the Company reached out to the US FDA with the proposal to include facial paralysis (including Bell's palsy) to the post-marketing Adverse Reactions section in the EUA Fact Sheet.

Myocarditis/Pericarditis

On 31 March 2023, EU/EMA was notified of an Internally-identified Significant Safety Issue (IISS) of myocarditis and pericarditis classified as an Emerging Safety Issue (ESI).

Summary of Significant Safety Issue:

The Company performed a full analysis of the available, latest safety data for myocarditis and pericarditis. Overall, the available safety data from post-authorisation sources (including an updated age and sex stratified RWE rapid cycle analysis (RCA) show an increase in the risk for myocarditis and pericarditis following Ad26.COV2.S vaccination, particularly in younger males under the age of 40 in the first 2 weeks following vaccination, with the highest risk at 7 days.

Actions taken:

Whilst the mechanism of action is not clearly established, the potential impact to public health of this disease and consistency of data justifies adding it as a safety concern for the vaccine, as an IIR in the cRMP.

A CCDS update to the Warnings and Precautions and the Adverse Reactions sections will be implemented. The full evaluation is found in Appendix 7.2.

Analysis

Request: On 08 March 2023, the US FDA communicated that the US Fact Sheets should be amended to reflect an elevated risk of myocarditis and pericarditis. Therefore, the Company conducted a comprehensive review based on the latest totality of the data which includes datamining of post-marketing data using disproportionality statistics in the Company global safety database, VAERS, the World Health Organization (WHO) VigiBase, the European Medicines Agency (EMA) EudraVigilance, case review of both clinical trial data and spontaneous cases reported in the Company global safety database, real world evidence (RWE) RCA, and observed versus expected (O/E) analysis.

MAH Conclusion: Based on the totality of data, particularly the most recent age and sex stratified RWE RCA outcome, myocarditis and pericarditis are considered ADRs (both assigned a reporting frequency of very rare) and an important identified risk (IIR) associated with the use of Ad26.COV2.S. Key factors supporting this conclusion include:

- A potential mechanism of action hypothesising hypersensitivity reaction to circulating Spike protein compared to healthy vaccinated individuals following mRNA vaccines, may be applicable to Ad26.COV2.S.
- Although no disproportionality was observed in VAERS or WHO VigiBase at either High Level Term (HLT) or PT levels, disproportionality was observed myocarditis and pericarditis in the Company global safety database and EudraVigilance.
- For the post-marketing spontaneous cases, most of the cases were assessed as Brighton Collaboration (BC) Level 4 and Level 5, indicating cases providing insufficient information to meet Level 1, 2, or 3, or there were clear alternative explanation to explain the event onset. However, several BC Level 1 to 3 cases were reported in close temporal association to the vaccine for which causality could not be excluded, and in particular, several BC level 2 cases that were reported among males under 40 years of age.
- The restricted O/E analysis for myocarditis indicated statistically significant differences in observed counts following exposure with Ad26.COV2.S for most, though not all, females and males in the 18 to 29, 30 to 39, 40 to 49, and 50 to 64 age groups in the US and EU, across the 3 risk windows. This was found more consistently in the male groups. The restricted O/E analysis for pericarditis indicated a statistically significant difference in observed counts following exposure with Ad26.COV2.S for only the US female 30 to 39 age group in the 1 to 7 day risk window.
- The RWE RCA indicates a high level of certainty of an increased risk of myocarditis and pericarditis for males aged 18 to 39 years post vaccination with Ad26.COV2.S. The increased risk was observed consistently across all 3 US claims databases and between different methods (i.e., a Self-Controlled Case Series and comparative cohort) as well as different risk windows.

The global spontaneous reporting rate of myocarditis and pericarditis for primary dose vaccination (cases of BC levels 1 to 4) was estimated at 4.32 and 4.15, respectively, per million doses administered; the assigned frequency category is: very rare.

The global spontaneous reporting rate of myocarditis and pericarditis for booster dose vaccination (cases of BC levels 1 to 4) was estimated at 4.47 and 2.55, respectively, per million doses administered; the assigned frequency category is: very rare.

Additional information on the analysis can be found in in Appendix 7.2

15. OVERVIEW OF SIGNALS: NEW, ONGOING, OR CLOSED

15.1. Ongoing Signals

The following signals are currently undergoing evaluation at DLD of this report. Additional details are provided in Appendix 3, Tabular Summary of Safety Signals That Were Ongoing or Closed During the Reporting Interval of this PBRER.

15.1.1. Cerebral Haemorrhage

On 12 December 2022, the event of cerebral haemorrhage with the use of Ad26.COV2.S was identified during a single case assessment. This signal is ongoing at the time of this PBRER's production.

Additional details are provided in Appendix 3, Tabular Summary of Safety Signals That Were Ongoing or Closed During the Reporting Interval of this PBRER.

15.1.2. Heavy Menstrual Bleeding

On 17 January 2023 the event of heavy menstrual bleeding with the use of Ad26.COV2.S was identified as a signal based on a statistical signal of disproportionate reporting within the Company global safety database. This signal is ongoing at the time of this PBRER's production.

Additional details are provided in Appendix 3, Tabular Summary of Safety Signals That Were Ongoing or Closed During the Reporting Interval of this PBRER.

15.1.3. Myocarditis/Pericarditis

On 14 February 2023, the US FDA requested the Company to update the US Fact Sheet with a warning and precaution for myocarditis and pericarditis. The Company conducted a comprehensive review of the most recent safety data including age and sex stratified RWE RCA during the preparation of this report. Based on the available safety data, the Company has considered myocarditis and pericarditis are ADRs associated with Ad26.COV2.S and categorised myocarditis and pericarditis as an IIR.

Additional information on the analysis can be found in Section 14, Late-Breaking Information and in Appendix 7.2.

15.1.4. Postural Orthostatic Tachycardia Syndrome

Request: In the second updated Pharmacovigilance Risk Assessment Committee (PRAC) Rapporteur Assessment report (AR) (PRAC AR 2023), (procedure number: EU EMEA/H/C/PSUSA/00010916/202208) for the 3rd Ad26.COV2.S PBRER (reporting period 25 February 2022 to 24 August 2022), circulated on 04 April 2023, the European Medicines Agency (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 co-morbidities. 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 in Appendix 7.3.

Note that POTS has been closed and the change in status will be reflected in the next scheduled PBRER.

The Company will continue to closely monitor events of POTS.

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

15.2.1. Myocardial Infarction

Request: On 18 May 2022, the Company received the following request from the Canadian Marketed Health Products Directorate following review of the first Bi-Monthly Safety Report for the Janssen COVID-19 vaccine (Ad26.COV2.S [recombinant]) covering the period of 01 November 2021 to 15 January 2022:

"*Provide a detailed Brighton Collaboration level criteria and causality assessment for myocardial infarction cases cumulatively up to the data lock point of the next PBRER. This cumulative review should include analyses of any additional cases, and an updated observed-to-expected analyses (stratified by age and gender, where possible).*

Include a summary of data from ongoing safety studies and relevant published literature in your response.

Provide a copy of the assessment of myocardial infraction and other safety signals identified by other regulators in the next PBRER."

MAH Conclusion: Based on review of the totality of available data, there is insufficient evidence to support a causal association between myocardial infarction (MI) and the Ad26.COV2.S vaccine. Key factors supporting this conclusion include lack of established biological plausibility, no

increased risk observed from review of a large clinical trial datasets, and insufficient evidence from aggregate post-marketing spontaneous reports as well as the biomedical literature. The Company will continue to monitor events of MI via routine PV activities.

Additional information on the analysis can be found in Appendix 7.4 and in Section 16.2.1.1.3 of the previous PBRER (25 February 2022 to 24 August 2022).

15.2.2. IgA Nephropathy

Request: In its assessment report on the Annual Renewal of the Conditional Marketing Authorisation for JCOVDEN covering the reporting period of 01 August 2021 to 31 July 2022; Addendum to Clinical Overview (ACO), (procedure number: EMEA/H/C/005737/R/0063), the Committee for Medicinal Products for Human use (CHMP) requested more details on the signal of Immunoglobulin A Nephropathy (IgA), that had been closed at the time of the ACO. Notably the CHMP requested the following (see Figure 1):

Figure 1: Committee for Medicinal Products for Human use (CHMP) request on the signal of IgA.

Immunoglobulin A (IgA) nephropathy: *in Appendix 3, a very short summary of this signal, which is not possible to evaluate.*

IgA Nephropathy	22/Feb/2022	NEW SIGNAL; CLOSED/ SAFETY ISSUE NOT-CONFIRMED	07/Mar/2022	Health Authority	On 22FEB2022 a signal was identified for the event of IgA Nephropathy with the use of COVID-19 VACCINE AD26.COV2.S based on a request from World Health Organization Uppsala Monitoring Centre.; 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 03MAR2022 (n=1 cases) reporting the following Medical Dictionary for Regulatory Activities Preferred Term: IgA Nephropathy. An analysis of relevant clinical trial data was performed.	Routine Pharmacovigilance Activities.

It is anticipated that this signal is presented in an evaluable form in the next PSUR.

MAH Conclusion: In the ACO with the reporting period covering 01 August 2021 to 31 July 2022, IgA nephropathy was succinctly presented as a signal closed during the reporting period. Following the submission of the ACO in the context of the renewal procedure, and in line with the request of CHMP, a cumulative ad-hoc analysis on glomerulonephritis and nephrotic syndrome, including IgA nephropathy has been presented in the 3rd PBRER with reporting dates of 25 February 2022 to 24 August 2022.

The cumulative ad-hoc analysis included all the 3 cases with IgA nephropathy received cumulatively. Therefore, presentation of the ad-hoc analysis in the 3rd PBRER, submitted after the ACO, addressed the above-mentioned request. The analysis concluded that based on the totality of the cumulative post-marketing and clinical trial data, and the comprehensive literature review, there is insufficient information to suggest an association between Ad26.COV2.S and the occurrence of glomerulonephritis and nephrotic syndrome.

In the second updated PRAC Rapporteur AR (PRAC AR 2023) for the 3rd PBRER (procedure number: EMEA/H/C/PSUA/0010916/202208), circulated on 04 April 2023, PRAC endorsed the MAH's conclusion on the analysis as follows:

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

Since the DLP of the 3rd PBRER (24 August 2022), and during the reporting period of the current PBRER (25 August 2022 to 24 February 2023), one further case with IgA nephropathy has been received in the Company global safety database. Assessment of this case, sourced from literature (Petrou) did not change previous conclusions on this topic, as it involved a small case series with several patients, including 1 patient who experienced nephrotic syndrome as a result of IgA nephropathy relapse without any further information on the patient's clinical course, medical history, concomitant medications, time to onset (TTO), and outcome of the events.

The Company will continue to monitor glomerulonephritis and nephrotic syndrome, including IgA nephropathy via routine pharmacovigilance activities.

15.2.3. Severe Cutaneous Adverse Reactions

Request: The second updated PRAC Rapporteur AR for the 3rd Ad26.COV2.S PBRER, (25 February 2022 to 24 August 2022), circulated on 04 April 2023, (procedure number: EMEA/H/C/PSUSA/000106/202208), (PRAC AR 2023) requested the Company address the following in the current PBRER:

"*Severe cutaneous adverse reactions have been evaluated in previous procedures, but there are some time periods which have not been reviewed. For the next PSUR, the period 25 February 2022 to 24 February 2023 should be specifically analysed, inclusive high-level analysis of post-marketing cases and the literature regarding SCAR.*"

Severe cutaneous adverse reactions (SCAR) are not listed in the CCDS (version 13, dated 28 June 2022) for Ad26.COV2.S or the current core Risk Management Plan (cRMP; version 6.0, dated 25 October 2022).

A cumulative review of SCAR through 24 February 2022 was previously conducted and included in the 3rd Ad26.COV2.S PBRER covering the reporting period of 25 February 2022 to 24 August 2022. The cumulative analysis found insufficient information to associate SCAR or erythema multiforme (EM) with the Ad26.COV2.S vaccine. Current review will provide a high-level analysis of post-marketing cases and the literature regarding SCAR from 25 February 2022 through 24 February 2023 to bridge up to the data gap from the previous cumulative review for the same topic.

MAH Conclusion: Combined with the previous cumulative review and this interval analysis, the Company found insufficient information to associate SCAR or EM with the Ad26.COV2.S vaccine. The Company will continue to monitor cases involving SCAR and EM via routine pharmacovigilance activities.

Additional information on the analysis can be found in Appendix 7.5.

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.

Trial VAC31518COV3005 is an ongoing randomised, double-blind, Phase 3 study to evaluate the safety, reactogenicity, and immunogenicity of the simultaneous administration of Ad26.COV2.S and the influenza vaccines in healthy adults 18 years of age and older. There were no safety concerns identified from this trial during the reporting period.

Methods

The Company global safety database was searched for medically confirmed and medically unconfirmed cases received during this reporting period and cumulatively which coded to the search criteria provided in Appendix 5.

Results/Discussion

Primary Dose

During this reporting period, a total of 17 (6 medically confirmed and 11 medically unconfirmed) post-marketing sources (including spontaneous and solicited), initial, primary dose cases reporting the use with concomitant vaccination were identified. There were 9 serious and 8 nonserious cases which reported a total of 107 events (58 serious, 49 nonserious).

Cumulatively, 114 (33 medically confirmed and 81 medically unconfirmed) post-marketing, primary dose cases reporting the use with concomitant vaccination were identified. There were 53 serious and 61 nonserious cases which reported a total of 588 events (188 serious, 400 nonserious).

The most frequently reported coadministered vaccine type (both during the reporting period as well as cumulatively) was the influenza vaccine (interval n=14; cumulatively n=70).

An overview of these cases is presented in Table 18 below.

Table 18: 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 Interval Reporting Period=17	Number of Cases Received Cumulatively=114[a]
Sex	Female	9	64
	Male	7	46
	NR	1	4
Age (Years)[b]	18 to 35	1	23
Minimum: 22	36 to 50	4	22
Maximum: 81	51 to 64	6	35
Mean: 55.9	≥65	4	27
Median: 55	NR	2	5
Source	Spontaneous	9	99
	Clinical study (noninterventional, solicited)	7	11
	Clinical study (noninterventional, unsolicited)	1	3
Country/Territory	United States	6	52
	Canada	5	7
	Germany	3	5
	Brazil	1	14
	Romania	1	1
	United Kingdom	1	1
Event Characteristics		**Number of Events=107**	**Number of Events=588**
Seriousness (Event Level)[c]	Serious	58	188
	Nonserious	49	400
Outcome (Event Level)[c]	Not resolved	45	159
	Resolving	32	115
	Resolved	11	119
	Fatal	1	15
	NR	18	173
Concomitant Vaccine Type[d]	Influenza vaccine	14	70
	Hepatitis B vaccine	2	11
	Diphtheria vaccine	1	8
	Hepatitis A vaccine	1	5
	Measles vaccine	1	2
	Mumps vaccine	1	2
	Other Vaccine	1	1
	Pertussis vaccine	1	8
	Pneumococcal vaccine	1	7
	Polio vaccine	1	3
	Rubella vaccine	1	3
	Tetanus vaccine	1	10

Key: NR=Not Reported

Table 18: 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 Interval Reporting Period=17	Number of Cases Received Cumulatively=114[a]

a: For the cumulative column, the counts were presented in decreasing order based on the current reporting period (25 August 2022 to 24 February 2023).
b: The median and mean age calculations were based on the current reporting period (25 August 2022 to 24 February 2023).
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 period (25 August 2022 to 24 February 2023). A single case may report more than 1 concomitant vaccine.

Of these 17 cases received, the most frequently reported countries/territories of origin (n≥3) were the US (n=6), Canada (n=5), and Germany (n=3). The cases concerned 9 females, 7 males, and 1 did not report sex. The age range was from 22 to 81 years.

The frequency distribution of the MedDRA PTs reported is presented in Table 19 below.

Table 19: 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 Interval Reporting Period[a]		Number of Events Reported Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
Headache	0	5	0	21
Fatigue	0	4	1	20
Pain in extremity	0	3	4	11
Ageusia	1	1	1	1
Arthralgia	0	2	1	11
COVID-19	0	2	0	8
Injection site pain	0	2	0	10
Nausea	1	1	1	6
Oropharyngeal pain	1	1	1	2
Pain	0	2	2	10
Pneumonia	2	0	3	0
Vaccination failure	2	0	15	0

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 and sorted by decreasing order for the reporting period (25 August 2022 to 24 February 2023). 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 period (25 August 2022 to 24 February 2023).

The events (≥3) included headache (n=5), fatigue (n=4), and pain in extremity (n=3). The mean and median TTO of all events were 140.8 and 41 days, respectively, and the range was from 0 to 607 days. Of the 107 EOI, outcomes were reported for 89 and are as follows: not resolved (n=45), resolving (n=32), resolved (n=11), and fatal (n=1). The fatal case concerned a 81-year-old female

with limited information who received concomitant influenza vaccine administration on an unspecified date and died from an unknown cause.

Of the 17 post-marketing cases reported, 6 had the dates of concomitant vaccine administration specified, with 4 cases documenting administration of the concomitant vaccine on the same day as Ad26.COV2.S. Of these 6 cases, 2 reported ageusia of which 1 case, occurred in the context of oral metastatic squamous cell carcinoma, while in the other case, there was limited information provided. Dates of vaccination were not specified for the remaining 11 cases. An overview of these cases is included in Table 20. Most of the events represent reactogenicity.

Table 20: Overview of MedDRA PTs in Post-marketing Primary Dose Cases Reporting Concomitant Vaccinations With the Use of Ad26.COV2.S (Cases=17)

MedDRA PTs	Number of Events[a]
Cases Reporting Specified Dates of Concomitant Vaccine Administration (n=6)	
Ageusia	2
Cases Reporting Unspecified Dates of Concomitant Vaccine Administration (n=11)	
Headache	5
Fatigue	4
Pain in extremity	3
Arthralgia	2
Injection site pain	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. MedDRA PTs with frequency ≥2 have been presented.

Booster Dose

During this reporting period, a total of 34 (8 medically confirmed and 26 medically unconfirmed) post-marketing, initial cases reported as booster were identified. There were 5 serious and 29 nonserious cases which reported a total of 208 events (17 serious, 191 nonserious). Of these cases, 29 were heterologous and 5 were homologous.

Cumulatively, 94 (16 medically confirmed and 78 medically unconfirmed) post-marketing cases reported as booster were identified. There were 31 serious and 63 nonserious cases which reported a total of 557 events (89 serious, 468 nonserious). Of these cases, 67 were heterologous and 27 were homologous.

The most frequently reported coadministered vaccine type (both during the reporting period as well as cumulatively) was the influenza vaccine (interval n=33; cumulatively n=89).

An overview of these cases is presented in Table 21 below.

Table 21: 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 Interval Reporting Period=34	Number of Cases Received Cumulatively=94[a]
Sex	Male	20	45
	Female	13	47
	NR	1	2
Age (Years)[b] **Minimum: 19** **Maximum: 86** **Mean: 51.7** **Median: 52**	18 to 35	7	10
	36 to 50	7	14
	51 to 64	10	32
	≥65	8	24
	Adult	1	2
	NR	1	8
Source	Clinical study (noninterventional, solicited)	24	31
	Spontaneous	10	60
Country/Territory	Germany	15	18
	Canada	9	9
	United States	6	30
	Brazil	1	30
	Netherlands	1	2
	Portugal	1	2
	United Kingdom	1	1
Classification	Heterologous	29	67
	Homologous	5	27
Event Characteristics		**Number of Events=208**	**Number of Events=557**
Seriousness (Event Level)[c]	Nonserious	191	468
	Serious	17	89
Outcome (Event Level)[c]	Resolved	83	163
	Resolving	44	130
	Not resolved	30	93
	NR	51	169
Concomitant Vaccine Type[d]	Influenza vaccine	33	89
	HPV vaccine	1	1

Key: HPV=Human Papillomavirus; NR=Not Reported

a: For the cumulative column, the counts were presented in decreasing order based on the current reporting period (25 August 2022 to 24 February 2023).

b: The median and mean age calculation were based on the current reporting period (25 August 2022 to 24 February 2023). 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 period (25 August 2022 to 24 February 2023).

Of these 34 post-marketing cases reported as booster, the most frequently reported countries/territories of origin (≥6) were Germany (n=15), Canada (n=9), and the US (n=6). These cases concerned 20 males, 13 females, and 1 did not report sex. The age range was from 19 to 86 years.

The frequency distribution of the MedDRA PTs reported in post-marketing cases reported as booster is presented in Table 22 below.

Table 22: 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 Period[a]		Number of Events Reported Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
Injection site pain	0	28	0	39
Fatigue	1	23	2	39
Headache	2	18	4	31
COVID-19 immunisation	0	12	0	13
Myalgia	1	9	1	15
Arthralgia	1	8	1	15
Malaise	1	8	1	16
Off label use	0	9	0	35
Pyrexia	0	6	2	20
Chills	0	5	1	14
COVID-19	1	4	3	11
Injection site swelling	0	5	0	7
Pain in extremity	0	5	0	10

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

a: The MedDRA PTs with a frequency ≥5 have been presented. The MedDRA PTs are sorted by decreasing order for the current reporting period (25 August 2022 to 24 February 2023). 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 period (25 August 2022 to 24 February 2023).

The most frequently (n≥10) reported events included injection site pain (n=28), fatigue (n=24), headache (n=20), COVID-19 immunisation (n=12), and myalgia (n=10). The mean and median TTO were 44.1 days and 1 day, respectively, and the range was from 0 to 304 days. Of the 208 EOI, outcomes were reported for 157 and are as follows: resolved (n=83), resolving (n=44), and not resolved (n=30).

Of the 34 post-marketing cases reported as booster, 14 had the dates of concomitant vaccine administration specified, of which 5 documented coadministration on the same day as Ad26.COV2.S. Dates of vaccination were not specified for the remaining 20 cases. An overview of events in these cases is included in Table 23. Most of the events represent reactogenicity.

Table 23: Overview of MedDRA PTs in Post-marketing Cases Reported as Booster Reporting Concomitant Vaccinations With the Use of Ad26.COV2.S (Cases=34)

MedDRA PTs	Number of Events[a]
Cases Reporting Specified Dates of Concomitant Vaccine Administration (n=14)	
Fatigue	10
Headache	9
Injection site pain	8
Malaise	7
Myalgia	6

Table 23: Overview of MedDRA PTs in Post-marketing Cases Reported as Booster Reporting Concomitant Vaccinations With the Use of Ad26.COV2.S (Cases=34)

MedDRA PTs	Number of Events[a]
COVID-19 immunisation	5
Cases Reporting Unspecified Dates of Concomitant Vaccine Administration (n=20)	
Injection site pain	20
Fatigue	14
Headache	11
COVID-19 immunisation	7
Arthralgia	6
Off label use	5

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 ≥5 have been presented.

Literature ICSR

No ICSR literature cases were received during the reporting period.

Line Listings

Death: During the current reporting period (25 August 2022 to 24 February 2023), a total of 1 fatal case was retrieved.

A CIOMS II LL of the fatal case is presented in Appendix 7.6.1. Additional information on the fatal case can also be found in Appendix 7.27, Death.

Booster: A cumulative CIOMS II LL of cases reported as booster is presented in Appendix 7.6.2.

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, including those with fatal outcome was observed. Based on review of all the available data, no safety concerns have been identified for use with concomitant vaccines during the reporting period.

15.4. Vaccination Anxiety-related Reactions

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, PRAC 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 7.7 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 Respiratory syncytial virus (RSV), Dengue virus, SARS-CoV-1, and Middle East Respiratory Syndrome Related Coronavirus (MERS-CoV).

Confirmed vaccination failure is defined as the occurrence of the specific vaccine preventable-disease in a person who is appropriately and fully vaccinated and taking into account the incubation period and the normal delay for the protection to be acquired as a result of immunisation. This definition requires clinical 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 period and cumulatively, which coded to the search criteria provided in Appendix 5.

In previous aggregate reports, the Company case definition of confirmed vaccination failure was as follows: medically confirmed, TTO >14 days, and positive COVID-19 testing. Suspected vaccination failure was defined as TTO >14 days, medically confirmed with no laboratory test results specified.

For the purposes of this analysis, all medically confirmed cases with a TTO >14 days and reporting a preferred term 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 preferred term are also reported], and Virologic failure or laboratory finding of positive polymerase chain reaction (PCR) test confirming COVID-19 positivity were considered as confirmed vaccination failure. 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 failure.

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 EOI for this topic.

Results/Discussion

Post-marketing Sources Cases

Primary Dose

During this reporting period, a total of 1,166 (1,061 medically confirmed and 105 medically unconfirmed) post-marketing, initial, primary dose cases reporting events of vaccine failure or LOE were identified. There were 1,093 serious and 73 nonserious cases which reported a total of 2,177 EOI (1,992 serious, 185 nonserious).

Cumulatively, 15,038 (12,537 medically confirmed and 2,501 medically unconfirmed) post-marketing, primary dose cases reporting events of vaccine failure or LOE were identified. There were 13,240 serious and 1,798 nonserious cases which reported a total of 26,763 EOI (23,862 serious, 2,901 nonserious).

An overview of these cases is presented in Table 24 below.

Table 24: Characteristics of Post-marketing Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Vaccine Failure, Lack of Efficacy/Effectiveness

Case Characteristics		Number of Cases Received During the Interval Reporting Period=1,166	Number of Cases Received Cumulatively=15,038[a]
Sex	Male	639	8,204
	Female	473	5,521
	NR	54	1,313
Age (Years)[b]	18 to 35	497	6,199
Minimum: 18	36 to 50	321	4,170
Maximum: 100	51 to 64	196	2,548
Mean: 40.1	≥65	79	1,042
Median: 38	Neonate	1	11
	Infant	1	3
	Adult	7	55
	NR	64	974
Sources	Spontaneous	1,145	14,872
	Clinical study (noninterventional, solicited)	18	160
	Clinical study (noninterventional, unsolicited)	3	6
Country/Territory	Austria	896	9,672
	United States	126	2,166
	Portugal	84	643
	Greece	18	71
	Canada	10	39
	Germany	9	378
	South Africa	8	72
	Brazil	4	107
	Philippines	3	278

Table 24: Characteristics of Post-marketing Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Vaccine Failure, Lack of Efficacy/Effectiveness

Case Characteristics		Number of Cases Received During the Interval Reporting Period=1,166	Number of Cases Received Cumulatively=15,038[a]
	Switzerland	3	14
	Belgium	2	64
	Czech Republic	1	17
	Netherlands	1	66
	Ukraine	1	2
Event Characteristics		**Number of Events=2,177**	**Number of Events=26,763**
Seriousness Criteria (Event Level)[c]	Other medically important condition	1,915	22,136
	Hospitalisation	53	1,075
	Death	11	351
	Life-threatening	9	270
	Disability	4	30
	Nonserious	185	2,901
Seriousness (Event Level)[c]	Serious	1,992	23,862
	Nonserious	185	2,901
Outcome (Event Level)[c]	Resolved	53	1,058
	Not resolved	25	778
	Fatal	11	351
	Resolving	9	505
	Resolved with sequelae	1	10
	NR	2,078	24,061

Key: NR=Not Reported

a: For the cumulative column, the counts were presented in decreasing order based on the current reporting period (25 August 2022 to 24 February 2023).

b: The median and mean age calculation were based on the current reporting period (25 August 2022 to 24 February 2023). Age group was presented for cases where age was not reported.

c: Seriousness criteria, seriousness, and outcome have been presented for the events of interest. A single case may report more than 1 event.

Of these 1,166 cases received, the most frequently reported countries/territories of origin (≥10) were Austria (n=896), the US (n=126), Portugal (n=84), Greece (n=18), and Canada (n=10). These cases concerned 639 males, 473 females, and 54 did not report sex. The age range was from 18 to 100 years.

The frequency distribution of the MedDRA PTs of interest reported is presented in Table 25 below.

Table 25: Frequency Distribution of MedDRA PTs in Post-marketing Primary Dose Cases Reporting Vaccine Failure, Lack of Efficacy/Effectiveness With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Received During the Interval Reporting Period[a]		Number of Events Received Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
Vaccination failure	998	0	12,063	0
COVID-19	929	60	10,473	941
SARS-CoV-2 test positive	14	81	252	1,153
Suspected COVID-19	7	33	139	662
Thrombosis with thrombocytopenia syndrome	11	0	86	0
Drug ineffective	9	0	187	3
Therapy non-responder	6	0	198	2
COVID-19 pneumonia	5	0	220	0
Post-acute COVID-19 syndrome	2	3	10	11

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

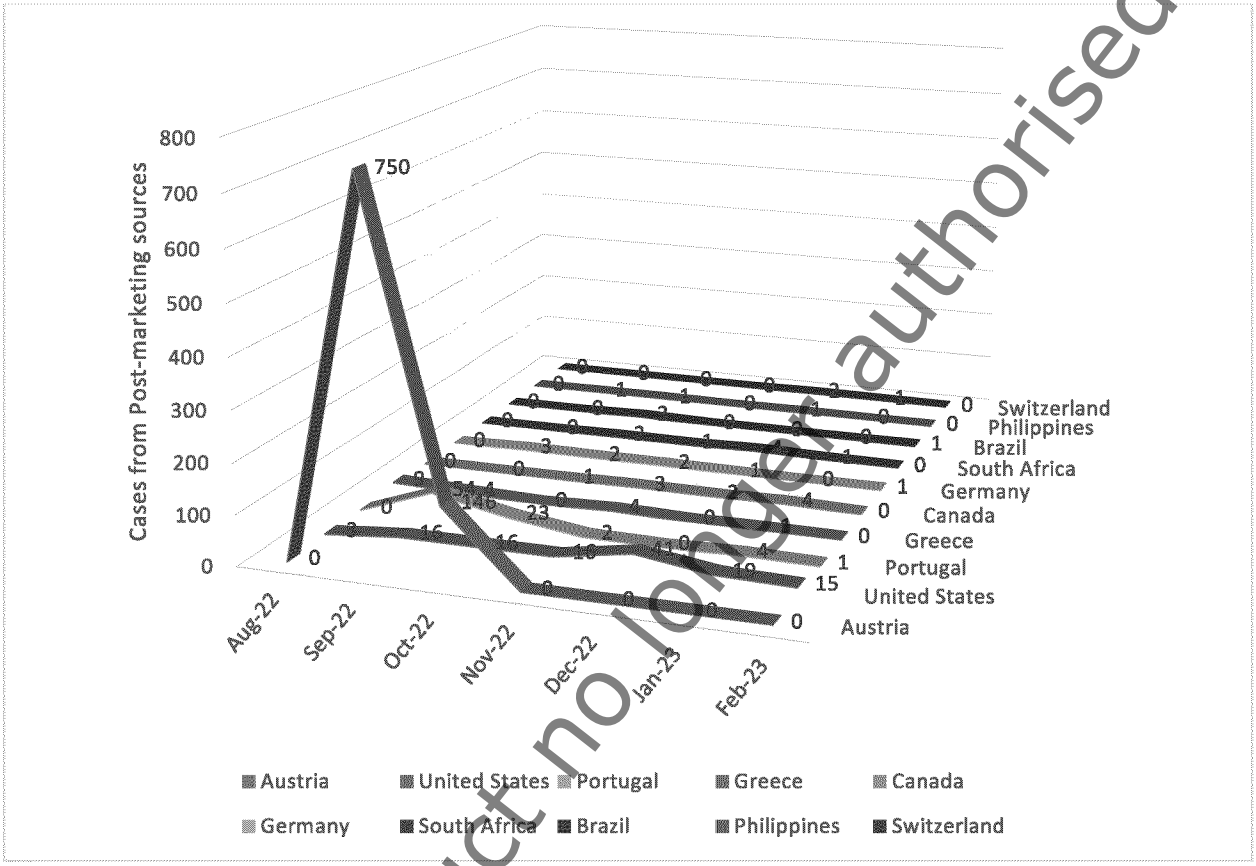
a: The MedDRA PTs of interest with a frequency ≥5 have been presented and sorted by decreasing order for the reporting period (25 August 2022 to 24 February 2023). A single case may report more than 1 MedDRA PT.

b: For the cumulative column, the counts were presented in decreasing order based on the current reporting period (25 August 2022 to 24 February 2023).

The EOI (≥5) included vaccination failure (n=998), COVID-19 (n=989), SARS-CoV-2 test positive(n=95), suspected COVID-19 (n=40), thrombosis with thrombocytopenia syndrome (n=11), drug ineffective (n=9), therapy non-responder (n=6), and COVID-19 pneumonia and post-acute COVID-19 syndrome (n=5 each). The mean and median TTO were 126 days and 121 days respectively and the range was from 0 to 687 days. Of the 2,177 EOI, outcomes were reported for 99 and are as follows: resolved (n=53), not resolved (n=25), fatal (n=11), resolving (n=9), and resolved with sequelae (n=1).

Figure 2 below depicts primary dose cases reporting vaccine failure, lack of efficacy/effectiveness involving the use of Ad26.COV2.S from the top 10 countries/territories by month.

Figure 2: Post-marketing Primary Dose Cases Reporting Vaccine Failure, Lack of Efficacy/Effectiveness With the Use of Ad26.COV2.S From the Top 10 Countries/Territories by Month (Period: 25 August 2022 to 24 February 2023)



The TTO reported in these 1,166 cases is presented in Table 26.

Table 26: Time to Onset in Post-marketing Primary Dose Cases Reporting Vaccine Failure, Lack of Efficacy/Effectiveness With the Use of Ad26.COV2.S (Cases=1,166)

TTO	Number of Cases
≤14 days	19
>14 days but ≤28 days	2
>28 days	1,031
NA[a]	2
NR	112
Total	**1,166**

Key: NA=Not Applicable; NR=Not Reported; TTO=Time to Onset

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

Of the total 1,166 cases received during the interval, 1,003 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. None 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.[17] Cases and events of confirmed vaccination failure are described in Table 27 below.

Table 27: Events of Confirmed Vaccination Failure in Post-marketing Primary Dose Cases Involving the Use of Ad26.COV2.S (Cases=1,003; Events=1,989)

Confirmed Vaccination Failure (Cases=1,003)	
Preferred Term	**Number of Events**
Vaccination failure	980
COVID-19	918
SARS-CoV-2 test positive	86
Asymptomatic COVID-19	2
COVID-19 pneumonia	1
Post-acute COVID-19 syndrome	1
SARS-CoV-2 test[a]	1
Total Confirmed COVID-19 events	**1,989**

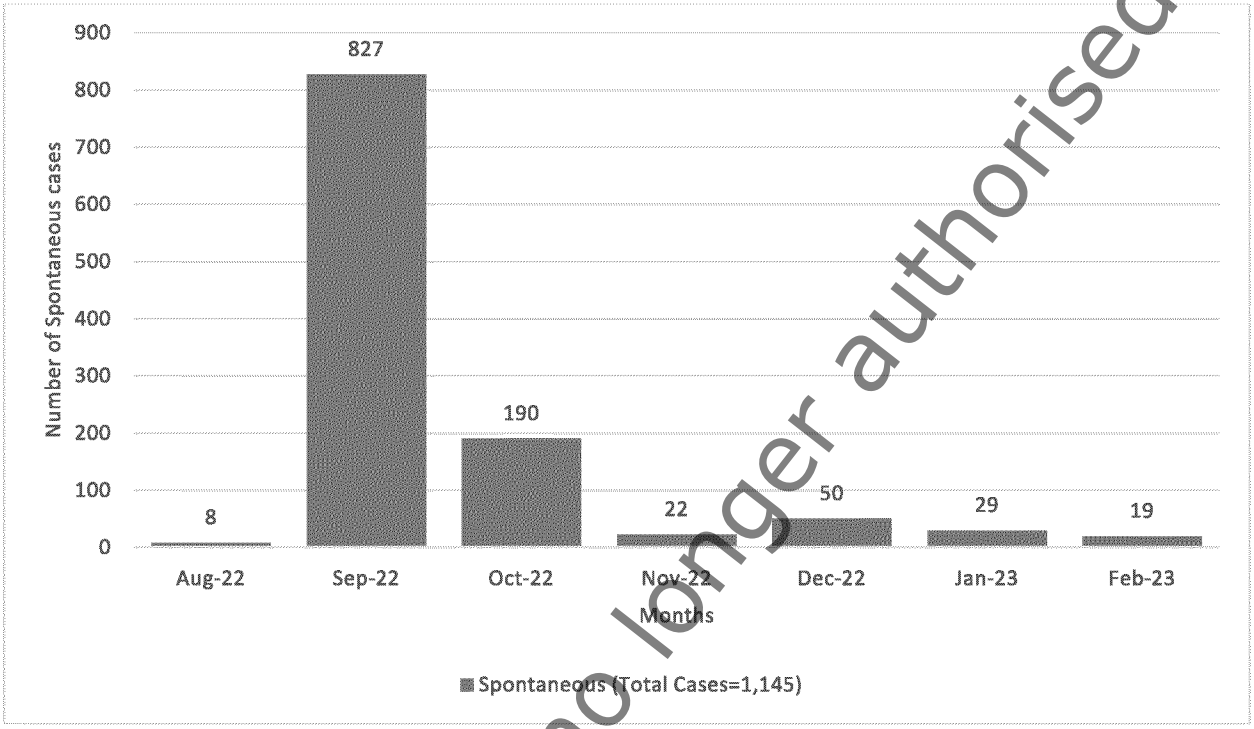
Key: COVID-19=Coronavirus Disease-2019; EOI=Event(s) of Interest; SARS-CoV-2=Severe Acute Respiratory Syndrome Coronavirus 2

a: One case reporting an EOI of "SARS-CoV-2 test" also reported an additional EOI of "Asymptomatic COVID-19"; hence, it has been included under confirmed vaccination failure.

Figure 3 depicts the case count of primary dose spontaneous cases by month involving the use of Ad26.COV2.S and reporting vaccine failure, lack of efficacy/effectiveness from 25 August 2022 to 24 February 2023.

[17] One case reporting an EOI of "SARS-CoV-2 test" also reported an additional EOI of "Asymptomatic COVID-19"; hence, it has been included under confirmed vaccination failure.

Figure 3: Case Count of Post-marketing Primary Dose Spontaneous Cases by Month Reporting Vaccine Failure, Lack of Efficacy/Effectiveness With the Use of Ad26.COV2.S (Period: 25 August 2022 to 24 February 2023).



The events are further sorted by seriousness and their respective outcomes in Table 28 and Table 29.

Table 28: Serious MedDRA PTs and Their Outcomes in Post-marketing Primary Dose Cases Reporting Vaccine Failure, Lack of Efficacy/Effectiveness With the Use of Ad26.COV2.S (Events=1,992)

MedDRA PTs	Number of Event Outcomes					
	Fatal	Not Resolved	Resolved	Resolving	NR	Total Number of Events[a]
Vaccination failure	0	1	8	0	989	998
COVID-19	5	4	7	0	913	929
SARS-CoV-2 test positive	4	0	7	0	3	14
Thrombosis with thrombocytopenia syndrome[b]	1	0	0	1	9	11
Drug ineffective	0	1	0	0	8	9
Suspected COVID-19	0	0	0	0	7	7
Therapy non-responder	0	0	0	0	6	6
COVID-19 pneumonia	0	0	0	0	5	5

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 ≥5 have been presented.

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

Table 29: Nonserious MedDRA PTs and Their Outcomes in Post-marketing Primary Dose Cases Reporting Vaccine Failure, Lack of Efficacy/Effectiveness With the Use of Ad26.COV2.S (Events=185)

MedDRA PTs	Number of Event Outcomes					
	Not Resolved	Resolved	Resolved With Sequelae	Resolving	NR	Total Number of Events[a]
SARS-CoV-2 test positive	2	6	0	1	72	81
COVID-19	4	14	0	2	40	60
Suspected COVID-19	4	8	0	3	18	33
Post-acute COVID-19 syndrome	1	0	0	0	2	3
SARS-CoV-2 antibody test	2	0	0	0	0	2
SARS-CoV-2 test negative	1	1	0	0	0	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 period, a total of 249 (82 medically confirmed and 167 medically unconfirmed) post-marketing, initial cases reported as booster were identified. There were 134 serious and 115 nonserious cases which reported a total of 344 EOI (165 serious, 179 nonserious). Of these cases, 138 were heterologous and 111 were homologous.

Cumulatively, 885 (297 medically confirmed and 588 medically unconfirmed) cases reported as booster were identified. There were 493 serious and 392 nonserious cases which reported a total of 1,277 EOI (570 serious, 707 nonserious). Of these cases, 536 were heterologous and 349 were homologous.

An overview of these cases reporting booster dose is presented in Table 30 below.

Table 30: Characteristics of Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Vaccine Failure, Lack of Efficacy/Effectiveness

Case Characteristics		Number of Cases Received During the Interval Reporting Period=249	Number of Cases Received Cumulatively=885[a]
Sex	Female	107	394
	Male	86	303
	NR	56	188
Age (Years)[b]	18 to 35	27	144
	36 to 50	42	193

Table 30: Characteristics of Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Vaccine Failure, Lack of Efficacy/Effectiveness

Case Characteristics		Number of Cases Received During the Interval Reporting Period=249	Number of Cases Received Cumulatively=885[a]
Minimum: 20 **Maximum: 96** **Mean: 53.9** **Median: 55**	51 to 64	48	202
	≥65	51	141
	Infant	1	1
	Adult	3	7
	Elderly	4	6
	NR	73	191
Sources	Spontaneous	206	792
	Clinical study (noninterventional, solicited)	36	69
	Clinical study (noninterventional, unsolicited)	7	24
Country/Territory[c]	United States	150	536
	Canada	26	48
	Austria	25	38
	Brazil	13	71
	Germany	11	32
	Greece	9	10
	Belgium	3	5
	Poland	2	3
	South Africa	2	4
Event Characteristics		**Number of Events=344**	**Number of Events=1,277**
Seriousness Criteria (Event Level)[d]	Other medically important condition	129	474
	Hospitalisation	25	67
	Death	7	17
	Life-threatening	4	11
	Nonserious	179	707
Seriousness (Event Level)[d]	Serious	165	570
	Nonserious	179	707
Outcome (Event Level)[d]	Not resolved	56	181
	Resolved	33	156
	Resolving	32	116
	Fatal	7	17
	NR	216	806

Key: NR=Not Reported

a: For the cumulative column, the counts were presented in decreasing order based on the current reporting period (25 August 2022 to 24 February 2023).

b: The median and mean age calculations were based on the current reporting period (25 August 2022 to 24 February 2023). 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 period.

d: Seriousness criteria, seriousness and outcome have been presented for the events. A single case may report more than 1 event.

Of these 249 cases reported as booster, the most frequently reported countries/territories of origin (≥11) were the US (n=150), Canada (n=26), Austria (n=25), Brazil (n=13), and Germany (n=11). These cases concerned 86 males, 107 females, and 56 did not report sex. The age range was from 20 to 96 years.

The frequency distribution of the MedDRA PTs reported in cases reported as booster is presented in Table 31 below.

Table 31: Frequency Distribution of MedDRA PTs in Post-marketing Cases Reported as Booster and Reporting Vaccine Failure, Lack of Efficacy/Effectiveness

MedDRA PTs	Number of Events Received During the Interval Reporting Period[a]		Number of Events Received Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
COVID-19	46	107	95	353
Vaccination failure	80	0	359	0
Suspected COVID-19	13	62	24	214
SARS-CoV-2 test positive	6	7	14	114
Drug ineffective	12	0	29	0
COVID-19 pneumonia	4	0	16	0
Asymptomatic COVID-19	0	2	2	8
Therapy non-responder	2	0	18	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

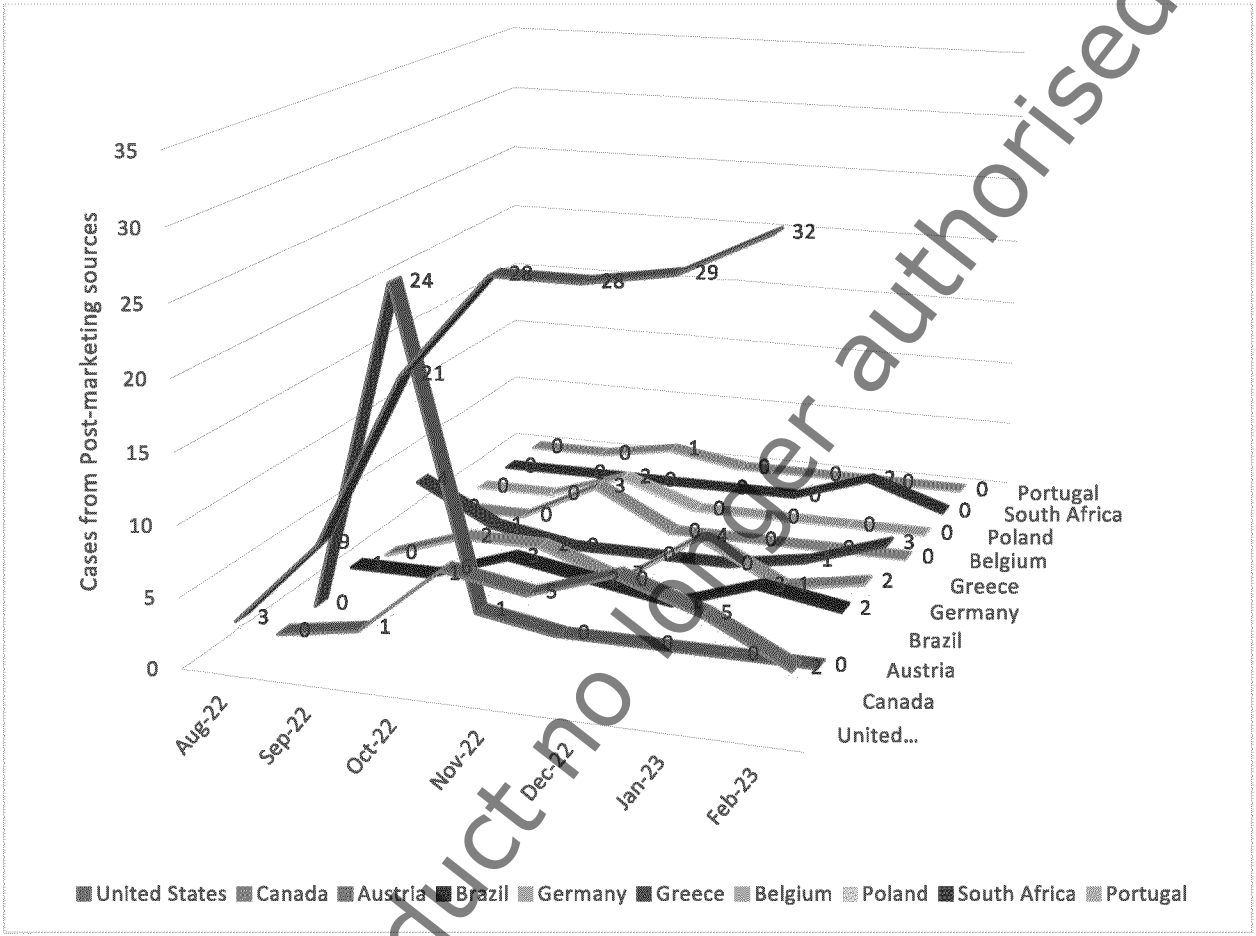
a: The MedDRA PTs of interest with a frequency ≥2 have been presented and are sorted by decreasing order for the current reporting period (25 August 2022 to 24 February 2023). A single case may report more than 1 MedDRA PT.

b: For the cumulative column, the counts were presented in decreasing order based on the current reporting period (25 August 2022 to 24 February 2023).

The EOI (≥2) included COVID-19 (n=153), vaccination failure (n=80), suspected COVID-19 (n=75), SARS-CoV-2 test positive (n=13), drug ineffective(n=12), COVID-19 pneumonia (n=4), and asymptomatic COVID-19 and therapy non-responder (n=2 each). The mean and median TTO were 280.4 and 218.5 days, respectively and the range is from 0 to 698 days. Of the 344 EOI, outcomes were reported for 128 and are as follows: not resolved (n=56), resolved (n=33), resolving (n=32), and fatal (n=7).

Figure 4 below depicts the cases reported as booster from the top 10 countries/territories by month.

Figure 4: Post-marketing Cases Reported as Booster and Reporting Vaccine Failure, Lack of Efficacy/Effectiveness With the Use of Ad26.COV2.S From the Top 10 Countries/Territories by Month (Period: 25 August 2022 to 24 February 2023)



The TTO reported for the 249 cases is presented in Table 32.

Table 32: Time to Onset in Post-marketing Cases Reported as Booster and Reporting Vaccine Failure, Lack of Efficacy/Effectiveness (Cases=249)

TTO	Number of Cases
≤14 days	6
>14 days but ≤28 days	2
>28 days	113
NA[a]	1
NR	127
Total	**249**

Key: NA=Not Applicable; NR=Not Reported; TTO=Time to Onset

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

Of the total 249 cases reported as booster received during interval, 42 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 medically confirmed case with a TTO >14 days reported the PT Suspected COVID-19. Cases and events of confirmed vaccination

failure (n=42) and suspected vaccination failure (n=1) with booster doses are described in Table 33 below.

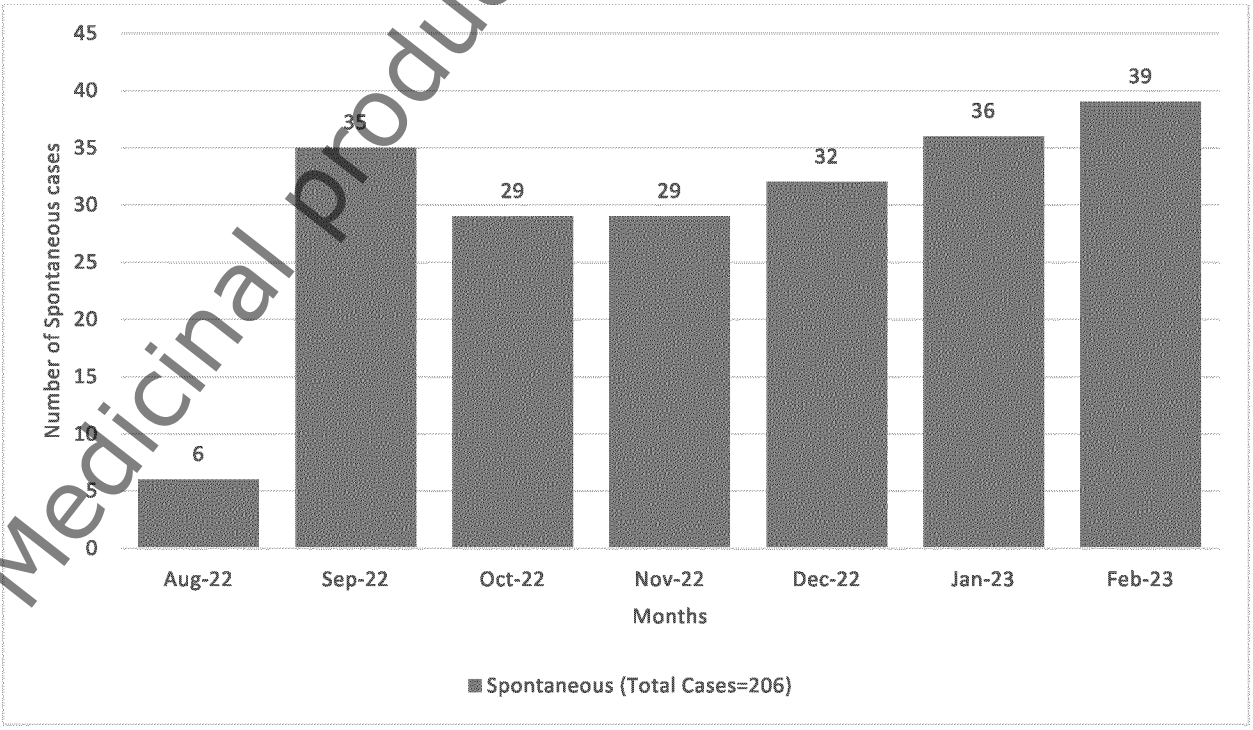
Table 33: Events of Confirmed and Suspected Vaccination Failure In Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S (Cases=43; Events=79)

Confirmed Vaccination Failure (Cases=42)	
Preferred Term	**Number of Events**
COVID-19	41
Vaccination failure	31
SARS-CoV-2 test positive	5
COVID-19 pneumonia	1
Total Confirmed COVID-19 events	**78**
Suspected Vaccination Failure (Cases=1)	
Preferred Term	**Number of Events**
Suspected COVID-19	1
Total Suspected COVID-19 events	**1**
Grand total	**79**

Key: COVID-19=Coronavirus Disease-2019; SARS-CoV-2=Severe Acute Respiratory Syndrome Coronavirus 2

Figure 5 depicts the monthly case count of spontaneous cases reported as booster from 25 August 2022 to 24 February 2023.

Figure 5: Case Count of Post-marketing Spontaneous Cases Reported as Booster Reporting Vaccine Failure, Lack of Efficacy/Effectiveness With the Use of Ad26.COV2.S (Period: 25 August 2022 to 24 February 2023)



The EOI are further sorted by seriousness and their respective outcomes in Table 34 and Table 35.

Table 34: Serious MedDRA PTs and Their Outcomes in Cases Reported as Booster Reporting Vaccine Failure, Lack of Efficacy/Effectiveness With the Use of Ad26.COV2.S (Events=165)

MedDRA PTs	Number of Event Outcomes					
	Fatal	Not Resolved	Resolved	Resolving	NR	Total Number of Events[a]
Vaccination failure	1	1	1	0	77	80
COVID-19	2	0	3	3	38	46
Suspected COVID-19	1	2	0	1	9	13
Drug ineffective	0	0	0	0	12	12
SARS-CoV-2 test positive	2	0	1	0	3	6
COVID-19 pneumonia	1	0	0	1	2	4
Therapy non-responder	0	0	0	0	2	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 35: Nonserious MedDRA PTs of Interest and Their Outcomes in Cases Reported as Booster Reporting Vaccine Failure, Lack of Efficacy/Effectiveness With the Use of Ad26.COV2.S (Events=179)

MedDRA PTs	Number of Event Outcomes				
	Not Resolved	Resolved	Resolving	NR	Total Number of Events
COVID-19	31	19	17	40	107
Suspected COVID-19	19	7	9	27	62
SARS-CoV-2 test positive	0	2	1	4	7
Asymptomatic COVID-19	0	0	0	2	2
Post-acute COVID-19 syndrome	1	0	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 Studies Cases

Information on Janssen Sponsored and Janssen Supported Clinical Studies cases can be found in Section 13, Lack of Efficacy in Controlled Clinical Trials and Section 17, Benefit Evaluation of the PBRER.

Literature ICSR

ICSR literature cases received during the current reporting period 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 period (25 August 2022 to 24 February 2023), a total of 23 fatal cases were retrieved. Of these cases, 11 reported a fatal EOI.

A CIOMS II LL of the fatal cases is presented in Appendix 7.8.1. Additional information on the fatal cases can also be found in Appendix 7.27, Death.

Booster: A cumulative CIOMS II LL of cases reported as booster is presented in Appendix 7.8.2.

Discussion

For the current reporting interval of 25 August 2022 to 24 February 2023, a total of 1,046 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 February 2022 to 24 August 2022 (n=4,631). This decrease in number is due to the overall decrease in reporting of vaccination failure/lack of efficacy cases in the current reporting period (total 1,415 cases) compared to the previous reporting period (total of 5,368 cases) which in turn may be due to the lower exposure to the vaccine compared to last reporting period.

Similarly, to the previous reporting interval, Austria continues to be the country with the highest number of cases, accounting for 76.8% of standard dose cases reported during the current interval. This increase continues to be related to proactive real-time surveillance by the Health Authority. The cases from Austria were received via line listings with minimal case data. A slight increase (approximately. 30 cases per month) was observed for vaccination failure cases following the booster dose in the US, primarily in the winter months where an increase in coronavirus cases was expected. No new cases reported events that were fatal, life-threatening, required hospitalisation, or were disabling.

Variant specific information from spontaneous sources has been included previously within the vaccine failure/lack of efficacy section, based on a EMA-PRAC request in the July 2021 monthly summary safety report assessment report. However, EMA-PRAC final assessment report for the Ad26.COV2.S PBRER covering the period of 25 August 2021 to 24 February 2022 has highlighted that limited information on SARS-CoV-2 variant is available from the reported cases. The Company has acknowledged and agreed with the Rapporteur's comment and has proposed not to pursue presentation of variant information in the vaccine failure section of the PBRER from spontaneous sources going forward as case counts are low and with limited information regarding variants, additionally there are other measures taken by the Company to assess variant specific data. Most current information available on vaccine efficacy and effectiveness is presented in Section 17, Benefit Evaluation.

Conclusion

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

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

15.6. Reactogenicity

Introduction

Reactogenicity is a standard topic for review in vaccine PBRERs. Reactogenicity is the physical manifestation of inflammatory response(s) to vaccination. These responses may include injection site pain, redness, swelling, or induration at the injection site. In addition, systemic symptoms may be observed such as fever, myalgia, or headache (Herve 2019).

Methods

The Company global safety database was searched for medically confirmed and medically unconfirmed cases received during this reporting period and cumulatively which coded to the search criteria provided in Appendix 5.

Reported events were further sorted into local reactogenicity versus systemic reactogenicity reactions. Local reactogenicity reactions included HLT of Administration site reactions Not Elsewhere Classified (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 period, a total of 34 (13 medically confirmed and 21 medically unconfirmed) post-marketing, initial, primary dose cases reporting serious AEs of reactogenicity were identified. These 34 cases reported a total of 75 serious EOI.

An overview of these cases is presented in Table 36 below.

Table 36: Characteristics of Post-marketing Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Reactogenicity

Case Characteristics		Number of Cases Received During the Interval Reporting Period=34	Number of Cases Received Cumulatively=1,489[a]
Sex	Female	13	805
	Male	21	667
Age (Years)[b]	18 to 35	6	451
	36 to 50	12	487

Table 36: Characteristics of Post-marketing Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Reactogenicity

Case Characteristics		Number of Cases Received During the Interval Reporting Period=34	Number of Cases Received Cumulatively=1,489[a]
Minimum: 19 **Maximum: 87** **Mean: 50.7** **Median: 50**	51 to 64 ≥65	10 6	348 172
Country/Territory	Germany	9	290
	United States	9	473
	South Africa	5	63
	Belgium	2	25
	Greece	2	38
	Ireland	1	28
	Korea, Republic of	1	104
	Lithuania	1	5
	Portugal	1	25
	Slovak Republic	1	4
	Spain	1	9
	Switzerland	1	6
Event Characteristics		**Number of Events=75**	**Number of Events=3,559**
Seriousness (Event Level)[c]	Serious	75	3,559
Outcome (Event Level)[c]	Not resolved	45	1,280
	Resolving	7	760
	Resolved	7	713
	Resolved with sequelae	3	101
	Fatal	3	74
	NR	10	631

Key: EOI=Event of Interest; NR=Not Reported

a: For the cumulative column, the counts were presented in decreasing order based on the current reporting period (25 August 2022 to 24 February 2023).

b: The median and mean age calculations were based on the current reporting period (25 August 2022 to 24 February 2023).

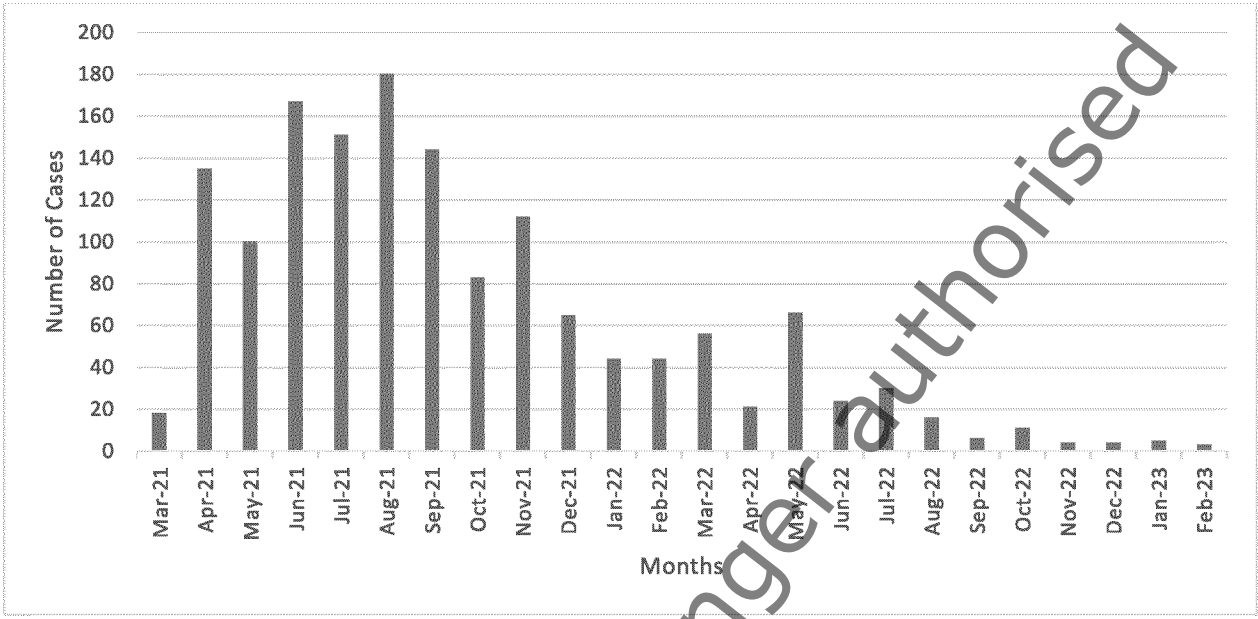
c: Seriousness and outcome have been presented for the EOI. A single case may report more than 1 EOI.

Of these 34 cases received, the most frequently reported countries/territories of origin (n≥2) were Germany, the US (n=9 each), South Africa (n=5), and followed by Belgium and Greece (n=2 each). The cases concerned 21 males and 13 females. The age range was from 19 to 87 years.

Cumulatively, 1,489 (671 medically confirmed and 818 medically unconfirmed) primary dose cases reporting reactogenicity were identified.

Figure 6 presents the number of doses received cumulatively by month (n=1,489).

Figure 6: Cumulative Case Reports by Month



Booster Dose

A total 4 (2 medically confirmed and 2 medically unconfirmed) post-marketing. initial cases reported as booster were identified. These 4 cases reported a total of 6 serious events. Of these cases, 1 was heterologous and 3 were homologous.

Cumulatively, 46 (14 medically confirmed and 32 medically unconfirmed) post-marketing cases reported as booster were identified.

An overview of these cases is presented in Table 37 below.

Table 37: Characteristics of Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Reactogenicity

Case Characteristics		Number of Cases Received During the Interval Reporting Period=4	Number of Cases Received Cumulatively=46[a]
Sex	Female	3	29
	Male	1	17
Age (Years)[b] **Minimum: 40** **Maximum: 71** **Mean: 50.8** **Median: 46**	36 to 50 ≥65	3 1	13 4
Sources	Spontaneous	3	41
	Clinical study (noninterventional, solicited)	1	4
Country/Territory	Germany	2	14
	United States	1	14
	Philippines	1	3

Table 37: Characteristics of Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Reactogenicity

Case Characteristics		Number of Cases Received During the Interval Reporting Period=4	Number of Cases Received Cumulatively=46[a]
Classification	Heterologous	1	21
	Homologous	3	25
Event Characteristics		**Number of Events=6**	**Number of Events=87**
Seriousness (Event Level)[c]	Serious	6	87
Outcome (Event Level)[c]	Fatal	2	2
	Resolved with sequelae	2	11
	Resolving	1	7
	Resolved	1	22

Key: EOI=Event(s) of Interest
a: For the cumulative column, the counts were presented in decreasing order based on the current reporting period (25 August 2022 to 24 February 2023).
b: The median and mean age calculations were based on the current reporting period (25 August 2022 to 24 February 2023).
c: Seriousness and outcome have been presented for the events of interest. A single case may report more than 1 EOI.

Of these 4 post-marketing cases reported as booster, the reported countries/territories of origin were Germany (n=2), and followed by the US and the Philippines (n=1 each). These cases concerned 1 male and 3 females. The age range was from 40 to 71 years.

Local Reactogenicity Reactions

Primary Dose

One post-marketing, initial, primary dose case reported 3 local reactogenicity reactions. This case concerned a 36-year-old female from [redacted] who experienced the serious EOI of vaccination site erythema, vaccination site pain, and vaccination site cellulitis. The outcome for all 3 events was reported as not resolved. The mean and median TTO was 3 days.

Cumulatively, 141 (46 medically confirmed and 95 medically unconfirmed) post-marketing primary dose cases reported local reactogenicity reactions.

Additionally, cases were reviewed to determine if there were any serious important identified (eg, [Thrombocytopenia with Thrombosis Syndrome {TTS}]), or important potential risk (eg [Immune Thrombocytopenia {ITP}]) events reported. This post-marketing primary dose case did not report any additional serious important identified or important potential risk events.

Booster Dose

During this reporting period, 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 (eg, TTS), or important potential risk (eg ITP) events reported. There were no post-marketing, initial booster cases retrieved to determine if there were any serious important identified or important potential risk events reported.

Systemic Reactogenicity Reactions

Primary Dose

All 34 post-marketing, initial, primary dose cases reported systemic reactogenicity reactions. The most frequently reported countries/territories of origin (n≥9) were Germany and the US (n=9 each). These cases concerned 21 males and 13 females. The age range was from 19 to 87 years.

Cumulatively, 1,466 (656 medically confirmed and 810 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 38 below. The event outcomes are presented in Table 39.

Table 38: Frequency Distribution of MedDRA PTs 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 Interval Reporting Period[a]	Number of Serious Events Received Cumulatively[b]
Headache	16	584
Fatigue	10	378
Dizziness	8	377
Pyrexia	8	427
Myalgia	7	240
Asthenia	6	157
Pain in extremity	4	168

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: The MedDRA PTs of interest with a frequency ≥4 have been presented and sorted by decreasing order for the reporting period (25 August 2022 to 24 February 2023). 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 period (25 August 2022 to 24 February 2023)

Table 39: Frequency Distribution of MedDRA PTs 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	Resolving	Resolved With Sequelae	Fatal	NR	Total Number of Serious Events
Headache	9	1	3	1	1	1	16
Fatigue	7	0	2	0	0	1	10
Dizziness	4	0	1	1	0	2	8
Pyrexia	4	1	0	1	2	0	8
Myalgia	5	0	0	0	0	2	7
Asthenia	2	2	1	0	0	1	6
Pain in extremity	3	0	0	0	0	1	4
Vomiting	3	0	0	0	0	0	3
Hypoaesthesia	2	1	0	0	0	0	3
Chills	0	2	0	0	0	0	2
Paraesthesia	1	0	0	0	0	1	2
Muscular weakness	2	0	0	0	0	0	2
Diarrhoea	0	0	0	0	0	1	1
Total	**42**	**7**	**7**	**3**	**3**	**10**	**72**

Key: MedDRA=Medical Dictionary for Regulatory Activities; n=Number; NR=Not Reported; PT=Preferred Term

The reported EOI (n≥4) were headache (n=16), fatigue (n=10); dizziness and pyrexia (n=8 each), myalgia (n=7), asthenia (n=6), and pain in extremity (n=4). The mean and median TTO were 2 days and 1 day respectively and the range was from 0 to 7 days. Of the 72 EOI, outcomes were reported for 62 and are as follows: not resolved (n=42); resolving and resolved (n=7 each), and resolved with sequelae and fatal (n=3 each).

In 1 case the fatal EOI was headache in association with fatal ischaemic stroke, in 1 case the EOI was pyrexia in association with sepsis, and 1 case concerned a 87-year-old, polymedicated male with underlying coronary disease, diabetes mellitus, and chronic kidney disease who started to experienced fever (39ºC) on the day of vaccination and was hospitalised. The patient experienced decreased oxygen saturation and died 12 days post-vaccination due to cardio-respiratory arrest. No results from diagnostic tests were provided.

Additionally, cases were reviewed to determine if there were any reported important identified (eg, TTS), or important potential risks (eg, ITP). Of these 34 cases, ITP (n=2), Guillain-Barré Syndrome (GBS; n=1), and TTS (n=1) were reported.

Booster Dose

A total 4 post-marketing, initial booster cases reported 6 systemic reactogenicity reactions. The reported countries/territories of origin were Germany (n=2), and followed by the US and the Philippines (n=1 each). These cases concerned 1 male and 3 females. The age range was from 40 to 71 years.

Cumulatively, 46 (14 medically confirmed and 32 medically unconfirmed) post-marketing booster cases reported systemic reactogenicity reactions. The frequency distribution of the serious MedDRA PTs of interest is presented in Table 40 below. The event outcomes are presented in Table 41.

Table 40: Frequency Distribution of MedDRA PTs in Post-marketing Cases Reported as Booster and Reporting Potential Systemic Reactogenicity Reactions With the Use of Ad26.COV2.S

MedDRA PTs	Number of Serious Events Received During the Interval Reporting Period[a]	Number of Serious Events Received Cumulatively[b]
Fatigue	2	11
Headache	2	19
Muscular weakness	1	3
Pyrexia	1	8

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

a: The MedDRA PTs of interest are sorted by decreasing order for the current reporting period (25 August 2022 to 24 February 2023). 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 period (25 August 2022 to 24 February 2023).

Table 41: Frequency Distribution of MedDRA PTs in Post-marketing Cases Reported as Booster and Their Outcomes for Potential Systemic Reactogenicity Reactions With the Use of Ad26.COV2.S

MedDRA PTs	Number of Event Outcomes				
	Resolved	Resolving	Resolved With Sequelae	Fatal	Total Number of Serious Events
Fatigue	0	0	1	1	2
Headache	1	0	0	1	2
Pyrexia	0	1	0	0	1
Muscular weakness	0	0	1	0	1
Total	**1**	**1**	**2**	**2**	**6**

Key: MedDRA=Medical Dictionary for Regulatory Activities; n=Number; NR=Not Reported; PT=Preferred Term.

The reported potential EOI were fatigue and headache (n=2 each), and pyrexia (n=1) and muscular weakness (in association with demyelinating polyneurpathy and microangiopathc leukoencephalopathy, n=1).

The mean and median TTO of the 6 EOI were 2.3 days and 2 days respectively, and the range was from 0 to 5 days. The reported outcomes were: fatal and resolved with sequelae (n= 2 each), and resolving and resolved (n=1 each). Both fatal EOI occurred in the same patient who experienced headache and fatigue in association with fatal cerebrovascular accident.

Additionally, cases were reviewed to determine if there were any reported important identified (eg, TTS), or important potential risks (eg, ITP). Of these 4 cases, GBS (n=1) was reported.

Clinical Trial Cases

During this reporting period, 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 reporting period.

Line Listings

Death: During the current reporting period (25 August 2022 to 24 February 2023), a total of 4 fatal cases reporting fatal events of reactogenicity were retrieved.

A CIOMS II LL of the fatal cases is presented in Appendix 7.9.1. Additional information on the fatal cases can also be found in Appendix 7.27, Death.

Booster: A cumulative CIOMS II LL of cases reported as booster is presented in Appendix 7.9.2.

Conclusion

The reported local and systemic 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 period have not shown any changes in terms of severity or outcome warranting changes to the prescribing information.

16. SIGNAL AND RISK EVALUATION

16.1. Summary of Safety Concerns

16.1.1. At the Beginning of the Reporting Period

The summary of safety concerns (ie, important identified risks, important potential risks, and missing information) at the beginning of the reporting period to be included in the Ad26.COV2.S PBRER are based on cRMP (version 5.0, dated 24 May 2022) and are summarised in Table 42.

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 4.2 (dated 12 July 2022).
- 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 in the PBRER based on GVP Module V - Risk Management Systems (Revision 2).

Table 42: Important Identified Risks, Important Potential Risks and Missing Information at the Beginning of the Reporting Period

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

Key: ITP=Immune Thrombocytopenia
a: Venous thromboembolism is an important identified risk in European Union Risk Management Plan version 4.2.
b: ITP is characterised in the European Union Risk Management Plan version 4.2 as Important Identified Risk "Thrombocytopenia, including ITP".

16.1.2. At the End of the Reporting Period

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

- The cRMP version 5.0 was updated to version 6.0 on 25 October 2022 with the reclassification of important potential risk of venous thromboembolism to an important identified risk.

The updated summary of safety concerns is presented below in Table 43.

Table 43: Important Identified Risks, Important Potential Risks and Missing Information at the End of the Reporting Period

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

Key: ITP=Immune thrombocytopenia
a: ITP is characterised in the European Union Risk Management Plan version 5.3 as Important Identified Risk "Thrombocytopenia, including ITP".

It should be noted that both the cRMP and the EU RMP are in the process of being updated with the inclusion of myocarditis and pericarditis as an IIR.

These updates are discussed under the appropriate subsections below in Sections 16.2 and 16.3.

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

16.2.1.1.1. Cutaneous Vasculitis

Request: On 01 September 2022, a signal was identified for the event cutaneous vasculitis (CV) with the use of COVID-19 vaccine Ad26.COV2.S based on a statistical signal of disproportionate reporting identified within the World Health Organization (WHO) VigiBase.

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

- no imbalance in reporting rate of the SMQ Vasculitis (narrow) was observed during the double-blind phase of the primary pooled analysis of 5 clinical studies (included over 38,500 subjects exposed to at least 1 dose of Ad2.COV2.S)
- insufficient evidence regarding the causal role of the Ad26.COV2.S vaccine and CV based on the review of post-marketing data
- only 1 out of 4 databases was disproportionately reported for PT of CV
- O/E analysis was not statistically significant across any age groups in the US and EU
- RWE RCA analysis indicated lack of evidence of increased risk of CV with Ad26.COV2.S
- although different mechanism of action (MOA) are proposed in the literature, no MOA is identified yet for the development of CV in association with Adenoviral vector COVID-19 vaccines.

The Company nevertheless acknowledges the existence of well documented cases in close temporal association for which causality to the vaccine could not be fully excluded based on the lack of other explanatory factors. The Company will continue to closely monitor cases of CV following Ad26.COV2.S. No further regulatory actions are currently considered.

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 period, there were no closed signals that were categorised as important identified risks. However, during the preparation of this report, the Company concluded a signal

evaluation on myocarditis and pericarditis. This signal has been categorised as an IIR (see Section 14, Late-breaking Information).

16.2.1.3. Closed Signals That are Categorised as Important Potential Risks

During this reporting period, there were no closed signals that were categorised as important potential risks.

16.2.1.4. Closed Signals That are Identified Risks not Categorised as Important

During this reporting period, there were no closed signals that were identified risks not categorised as important.

16.2.1.5. Closed Signals That are Potential Risks not Categorised as Important

During this reporting period, the following signals have been closed and are potential risks not categorised as important:

16.2.1.5.1. Transverse Myelitis

Request: On 07 December 2022, a signal of transverse myelitis (TM) with the use of Ad26.COV2.S was identified based on an internal review following routine signal detection activities, including literature article by Nguyen (2022), disproportionality analysis, and Real-World Data (RWD) RCA of US claims databases.

MAH Conclusion: Based on the totality of data, there is reasonable basis to consider TM as an ADR associated with Ad26.COV2.S. Key factors supporting this conclusion include:

- Biological plausibility for TM has not been established; however, there are proposed mechanisms including molecular mimicry and bystander activation which induces an immune response.
- Through the data mining activities, disproportionality in the Company global safety database, VigiBase, and EudraVigilance databases was observed. No disproportionality was observed in vaccine-only database (VAERS), possibly due to the overrepresentation of the term being listed for several other vaccines in the database.
- RWD RCA results suggested an increased risk of TM (relative risk ~2) after the first Ad26.COV2.S dose in the 1-to-42-day risk window. These results were consistent across analytic methods in 2 out of 3 data sources.
- The majority of 109 post-marketing primary dose and 3 booster dose cases identified from the Company global safety database reported EOI within the risk window of 1 to 42 days; 89 post-marketing primary dose and all 3 booster dose cases met BC criteria Level 2 to 4 of diagnostic certainty, of which 24 primary dose and 2 booster dose cases were at BC Level 2 to 3. In 13 primary dose and 1 booster dose cases causality to the vaccine could not be excluded due to the plausible temporal relationship and absence of clear alternative aetiologies or risk factors. Global spontaneous reporting rates for primary and booster doses (based on cases meeting BC Level 1 to 4) were 1.69 and 1.01 per million doses administered, respectively.

- The restricted sensitivity analysis showed an O/E ratio of >1 in both age groups (18 to 59 years and ≥60 years) in both regions (EU and US). The O/E ratio was statistically significant for all groups.
- Literature review (case reports and systematic reviews) indicated that TM was associated with various COVID-19 vaccines. The trigger article (Nguyen 2022), showed a possible association between both mRNA and vector based COVID-19 vaccines and TM with the highest point estimate observed for Ad26.COV2.S.

Inclusion of an AE as an ADR does not constitute an admission that medical personnel, user facility, holder of the regulatory licenses, distributor, manufacturer, or the product caused or contributed to a particular event. ADR determinations are not intended to be an appraisal of the medical cause of a particular event; instead, they represent an evaluation based on review of the available relevant information at the time of the evaluation according to the appropriate regulatory requirements.

Additional information on the analysis can be found in Appendix 7.11.

16.3. Evaluation of Risks and New Information

Effectiveness of Targeted follow-up questionnaires

In alignment with EU GVP Module V, the Company implemented specific follow-up questionnaires for certain events of special interest as part of its routine pharmacovigilance activities.

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, PRAC endorsed the discontinuation of targeted follow-up questionnaires (TFUQ) for TTS/VTE, VAED/VAERD and multisystemic inflammatory syndrome. These TFUQ will not be presented in this PBRER or in future PBRERs.

16.3.1. New Information on Important Identified Risks

16.3.1.1. Thrombosis With Thrombocytopenia Syndrome

Introduction

According to the cRMP (version 5.0; dated 24 May 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 period and cumulatively which coded to the search criteria provided in Appendix 5.

Results/Discussion

During this reporting period, a total of 23 (18 medically confirmed and 5 medically unconfirmed) initial, primary dose cases reporting TTS were retrieved. There were 22 serious and 1 nonserious case which reported a total of 67 EOI (63 serious, 4 nonserious).

During this reporting period, only 1 medically confirmed, initial (no medically unconfirmed) case reported as booster was identified. This serious, heterologous case reported 3 serious EOI.

Post-marketing Sources (Including Spontaneous and Solicited) Cases

Primary Dose

During this reporting period, a total of 22 (17 medically confirmed and 5 medically unconfirmed) post-marketing, initial, primary dose cases reporting TTS were retrieved. There were 22 serious cases which reported a total of 66 EOI (63 serious, 3 nonserious).

Cumulatively, 353 (273 medically confirmed and 80 medically unconfirmed) post-marketing, primary dose cases reporting TTS were retrieved. There were 352 serious and 1 nonserious case which reported a total of 1,405 EOI (1,388 serious, 17 nonserious).

An overview of these cases is presented in Table 44 below.

Table 44: Characteristics of Post-marketing Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Thrombosis With Thrombocytopenia Syndrome

Case Characteristics		Number of Cases Received During the Interval Reporting Period=22	Number of Cases Received Cumulatively=353[a]
Sex	Female	8	164
	Male	7	156
	NR	7	33
Age (Years)[b]	18 to 35	6	65
Minimum: 22	36 to 50	6	114
Maximum: 83	51 to 64	3	92
Mean: 46.8	≥65	3	46
Median: 48	NR	4	32
Source	Spontaneous	19	336
	Clinical study (noninterventional, solicited)	3	17
Country/Territory[c]	United States	9	195
	Greece	4	9
	Canada	3	3
	Germany	3	51

Table 44: Characteristics of Post-marketing Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Thrombosis With Thrombocytopenia Syndrome

Case Characteristics		Number of Cases Received During the Interval Reporting Period=22	Number of Cases Received Cumulatively=353[a]
Event Characteristics		**Number of Events=66**	**Number of Events=1,405**
Seriousness (Event Level)[d]	Serious	63	1,388
	Nonserious	3	17
Outcome (Event Level)[d]	Not resolved	15	454
	Resolving	7	143
	Fatal	3	210
	NR	41	458

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 period (25 August 2022 to 24 February 2023).

b: The median and mean age calculation were based on the current reporting period (25 August 2022 to 24 February 2023).

c: Countries/Territories with a frequency ≥3 were presented in decreasing order for the current reporting period (25 August 2022 to 24 February 2023).

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

Of these 22 cases received, the most frequently reported countries/territories of origin (n≥3) were the US (n=9), Greece (n=4), and followed by Canada and Germany (n=3 each). These cases concerned 7 males, 8 females, and 7 did not report sex. The age range was from 22 to 83 years.

The frequency distribution of the MedDRA PTs of interest reported is presented in Table 45 below.

Table 45: Frequency Distribution of MedDRA PTs in Post-marketing Primary Dose Cases Reporting Thrombosis With Thrombocytopenia Syndrome With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
Thrombosis with thrombocytopenia syndrome	11	0	98	0
Cerebral venous sinus thrombosis	5	0	89	0
Deep vein thrombosis	5	0	85	0
Transverse sinus thrombosis	4	0	16	0
Thrombotic thrombocytopenic purpura	4	0	15	0
Thrombocytopenia	4	0	199	0
Platelet count decreased	2	2	120	12

Table 45: Frequency Distribution of MedDRA PTs in Post-marketing Primary Dose Cases Reporting Thrombosis With Thrombocytopenia Syndrome With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
Pulmonary embolism	3	0	120	0
Superior sagittal sinus thrombosis	2	0	17	0
Portal vein thrombosis	2	0	26	0
Thrombosis	2	0	92	0
Jugular vein thrombosis	2	0	20	0
Sigmoid sinus thrombosis	2	0	6	0

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: The MedDRA PTs of interest with a frequency ≥2 have been presented and sorted by decreasing order for the reporting period (25 August 2022 to 24 February 2023). 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 period (25 August 2022 to 24 February 2023).

The EOI reported at a frequency ≥2 included thrombosis with thrombocytopenia syndrome (n=11), cerebral venous sinus thrombosis and deep vein thrombosis (n=5 each); transverse sinus thrombosis, thrombotic thrombocytopenic purpura, thrombocytopenia, and platelet count decreased (n=4 each); and pulmonary embolism (n=3); superior sagittal sinus thrombosis, portal vein thrombosis, thrombosis, jugular vein thrombosis, and sigmoid sinus thrombosis (n=2 each). The mean and median TTO were 111.3 and 23 days, respectively, and the range was from 10 to 467 days. Of the 66 EOI, outcomes were reported for 25 and are as follows: not resolved (n=15), resolving (n=7), and fatal (n=3).

Of these 22 cases, for the reporting period, the Company identified these 15 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 PRAC criteria (see Table 46).

Table 46: Number of Cases by Age and Sex and Working Case Definitions for Post-marketing Cases Reporting Thrombosis With Thrombocytopenia With the Use of Ad26. COV2.S Vaccine for the Reporting Period (Number of Cases=15; Number of Events=52)

Age Group (Years)	18 to 35			36 to 50			51 to 83		NR
Sex	F	M	NR	F	M	NR	F	M	NR
CDC									
Tier 1	1	0	3	1	0	1	1	0	0
Tier 2	0	0	0	0	0	0	0	0	1
Neither	1	1	0	1	2	0	0	1	1
Total	**2**	**1**	**3**	**2**	**2**	**1**	**1**	**1**	**2**
Brighton Collaboration									
Level 1	1	0	2	1	1	0	1	0	1
Level 2	0	0	0	0	0	0	0	0	0
Level 3	0	0	1	0	0	1	0	0	0
Level 4	1	1	0	1	0	0	0	0	1
Level 5	0	0	0	0	1	0	0	1	0
Total	**2**	**1**	**3**	**2**	**2**	**1**	**1**	**1**	**2**

Table 46: Number of Cases by Age and Sex and Working Case Definitions for Post-marketing Cases Reporting Thrombosis With Thrombocytopenia With the Use of Ad26. COV2.S Vaccine for the Reporting Period (Number of Cases=15; Number of Events=52)

Age Group (Years)	18 to 35			36 to 50			51 to 83		NR
PRAC									
Confirmed	0	0	2	0	0	1	0	0	0
Probable	0	0	1	0	0	0	0	0	0
Possible	2	1	0	2	2	0	1	0	2
Unlikely	0	0	0	0	0	0	0	1	0
Criteria not met	0	0	0	0	0	0	0	0	0
Total	**2**	**1**	**3**	**2**	**2**	**1**	**1**	**1**	**2**

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

Booster Dose

During this reporting period, 1 medically confirmed, post-marketing, initial, case reported as booster was identified. This heterologous case concerned a 33-year-old male from [redacted] who experienced the serious EOI of thrombosis with thrombocytopenia syndrome, cerebral venous sinus thrombosis, and haemorrhagic infarction. The TTO was not reported for any of the EOI and the reported outcomes were: unknown (n=2) and not resolved (n=1).

Cumulatively, 7 medically confirmed (no medically unconfirmed) cases reported as booster were identified. There were 7 serious cases which reported a total of 16 serious EOIs. Of these cases, 2 were heterologous and 5 were homologous.

Clinical Trial Cases

During this reporting period, only 1 clinical case (primary dose, no booster) was retrieved from Janssen Sponsored Studies and no cases were retrieved from Janssen Supported Clinical Studies

Janssen Sponsored Clinical Studies

During this reporting period, only 1 primary dose case reporting TTS was retrieved from a Janssen Sponsored Clinical Study. This case was reported from VAC31518COV3001 and concerned a male with an unknown age from [redacted] who experienced the nonserious event of thrombosis with thrombocytopenia syndrome. The TTO and outcome of the event were not reported.

During this reporting period, no cases reported as booster were retrieved from Janssen Sponsored Clinical Studies.

Janssen Supported Clinical Studies

During this reporting period, there were no cases were retrieved from Janssen Supported Clinical Studies.

Literature ICSR

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

Line Listings

Death: During the current reporting period (25 August 2022 to 24 February 2023), only 1 fatal case reporting a fatal EOI was retrieved.

A CIOMS II LL of the fatal case is presented in Appendix 7.12.1. Additional information on the fatal case can also be found in Appendix 7.27, 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 from other sources, the information is consistent with what is currently known about TTS.

16.3.1.2. Guillain-Barré Syndrome

Introduction

According to the cRMP (version 5.0; dated 24 May 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 period and cumulatively, which coded to the search criteria provided in Appendix 5.

Results/Discussion

During this reporting period, a total of 42 (14 medically confirmed and 28 medically unconfirmed) initial, primary dose cases reporting GBS were retrieved. All cases were serious and reported a total of 45 serious EOI.

During this reporting period, a total of 7 (4 medically confirmed and 3 medically unconfirmed) initial cases reported as booster were identified. All cases were serious and reported a total of 7 serious EOI. Of these cases, 5 were homologous and 2 were heterologous.

Post-marketing Sources (Including Spontaneous and Solicited) Cases

Primary Dose

During this reporting period, a total of 41 (13 medically confirmed and 28 medically unconfirmed) post-marketing, initial, primary dose cases reporting GBS were retrieved. All cases were serious and reported a total of 44 serious EOI.

Cumulatively, 625 (349 medically confirmed and 276 medically unconfirmed) post-marketing, primary dose cases reporting GBS were retrieved. All cases were serious and reported a total of 662 serious EOI.

An overview of these cases is presented in Table 47 below.

Table 47: 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 Interval Reporting Period=41	Number of Cases Received Cumulatively=625[a]
Sex	Male	22	370
	Female	14	222
	NR	5	33
Age (Years)[b]	18 to 35	8	71
Minimum: 20	36 to 50	12	174
Maximum: 80	51 to 64	10	239
Mean: 46.8	≥65	4	83
Median: 47.0	NR	7	51
Source	Spontaneous	40	624
	Clinical study (noninterventional, solicited)	1	1
Country/Territory[c]	United States	13	330
	South Africa	9	14
	Germany	5	89
	Belgium	2	7
	Netherlands	2	19
	Portugal	2	12
Event Characteristics		**Number of Events=44**	**Number of Events=662**
Seriousness (Event Level)[d]	Serious	44	662
Outcome (Event Level)[d]	Not resolved	14	312
	Resolving	9	119
	Resolved	3	35
	Fatal	2	6
	Resolved with sequelae	1	25

Table 47: 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 Interval Reporting Period=41	Number of Cases Received Cumulatively=625[a]
	NR	15	165

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 period (25 August 2022 to 24 February 2023).
b: The median and mean age calculation were based on the current reporting period (25 August 2022 to 24 February 2023).
c: Countries/territories with frequency ≥2 were presented in decreasing order for the current reporting period (25 August 2022 to 24 February 2023).
d: Seriousness and outcome have been presented for the events. A single case may report more than 1 EOI.

Of these 41 post-marketing primary dose cases received, the most frequently reported countries/territories of origin (n≥5) were the US (n=13), South Africa (n=9) and Germany (n=5). These cases concerned 22 males, 14 females, and 5 did not report sex. The age range was from 20 to 80 years.

The frequency distribution of the MedDRA PTs of interest reported is presented in Table 48 below.

Table 48: 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 Interval Reporting Period[a]		Number of Events Reported Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
Guillain-Barré syndrome	36	0	566	0
Chronic inflammatory demyelinating polyradiculoneuropathy	7	0	47	0
Demyelinating polyneuropathy	1	0	17	0

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: The MedDRA PTs of interest have been presented and sorted by decreasing order for the reporting period (25 August 2022 to 24 February 2023). 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 period (25 August 2022 to 24 February 2023).

The EOI included GBS (n=36), chronic inflammatory demyelinating polyradiculoneuropathy (n=7), and demyelinating polyneuropathy (n=1). The mean and median TTO were 53.2 and 18.0 days, respectively, and the range was from 0 to 324 days. Of the 44 EOI, outcomes were reported for 29 and are as follows: not resolved (n=14), resolving (n=9), resolved (n=3), fatal (n=2), and resolved with sequelae (n=1).

Booster Dose

During this reporting period, a total of 7 (4 medically confirmed and 3 medically unconfirmed) initial, post-marketing cases reported as booster were identified. All cases were serious and reported a total of 7 serious EOI. Of these cases, 5 were homologous and 2 were heterologous.

Cumulatively, 17 (5 medically confirmed and 12 medically unconfirmed) cases reported as booster were identified. All cases were serious and reported a total of 17 serious EOI. Of these cases, 10 were heterologous and 7 were homologous.

An overview of these cases is presented in Table 49 below.

Table 49: 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 Interval Reporting Period=7	Number of Cases Received Cumulatively=17[a]
Sex	Female	4	7
	Male	3	9
Age (Years)[b]	18 to 35	1	2
Minimum: 29	51 to 64	2	6
Maximum: 72	≥65	3	5
Mean: 58.0	NR	1	2
Median: 62.5			
Source	Spontaneous	6	16
	Clinical study (noninterventional, solicited)	1	1
Country/Territory	Germany	2	4
	Brazil	1	4
	Egypt	1	1
	Portugal	1	1
	South Africa	1	2
	United States	1	3
Classification	Homologous	5	7
	Heterologous	2	10
Event Characteristics		**Number of Events=7**	**Number of Events=17**
Seriousness (Event Level)[c]	Serious	7	17
Outcome (Event Level)[c]	Resolving	3	4
	Fatal	1	2
	Resolved with sequelae	1	1
	NR	2	6

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 period (25 August 2022 to 24 February 2023).

Table 49: 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 Interval Reporting Period=7	Number of Cases Received Cumulatively=17[a]

b: The median and mean age calculations were based on the current reporting period (25 August 2022 to 24 February 2023). Age group was presented for cases where age was not reported.
c: Seriousness and outcome have been presented for the EOI.

Of these 7 post-marketing cases reported as booster, the most frequently reported country/territory of origin (n≥2) was Germany (n=2). These cases concerned 4 females and 3 males. The age range was from 29 to 72 years.

The frequency distribution of the MedDRA PTs of interest reported in post-marketing cases reported as booster is presented in Table 50 below.

Table 50: 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 Interval Reporting Period[a]		Number of Events Reported Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
Guillain-Barré syndrome	3	0	13	0
Demyelinating polyneuropathy	2	0	2	0
Chronic inflammatory demyelinating polyradiculoneuropathy	1	0	1	0
Miller Fisher syndrome	1	0	1	0

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: The MedDRA PTs of interest have been presented and sorted by decreasing order for the current reporting period (25 August 2022 to 24 February 2023).
b: For the cumulative column, the events were presented in decreasing order based on the event counts of the current reporting period (25 August 2022 to 24 February 2023).

The EOI included GBS (n=3), demyelinating polyneuropathy (n=2), and chronic inflammatory demyelinating polyradiculoneuropathy and Miller Fisher syndrome (n=1 each). The mean and median TTO were 144.8 and 109.0 days, respectively, and the range was from 17 to 344 days. Of the 7 EOI, outcomes were reported for 5 and are as follows: resolving (n=3), and fatal and resolved with sequelae (n=1 each).

Clinical Trial Cases

During this reporting period, 1 clinical case (primary dose, no booster) was retrieved from a Janssen Sponsored Clinical Study and no cases were retrieved from Janssen Supported Clinical Studies.

Janssen Sponsored Clinical Studies

During this reporting period, 1 primary dose case reporting GBS was retrieved from a Janssen Sponsored Clinical Study. This case was reported from VAC31518COV3001 and concerned a 66-year-old female from [redacted] who experienced a serious EOI of GBS. The TTO was not reported and the outcome was reported as resolved.

During this reporting period, no cases reported as booster were retrieved from Janssen Sponsored Clinical Studies.

Literature ICSR

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

Line Listings

Death: During the current reporting period (25 August 2022 to 24 February 2023), a total of 5 fatal cases were retrieved. Of these cases, 3 reported a 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 7.27, 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 GBS.

16.3.1.3. Venous Thromboembolism

Introduction

Venous thromboembolism (VTE) has been reclassified as an important identified risk in the EU RMP.

According to the cRMP (version 5.0, dated 24 May 2022), VTE is an important potential risk associated with the use of Ad26.COV2.S. However, on 10 May 2022, based on the evidence from post-marketing data sources, the Company reclassified VTE from an important potential risk to an important identified risk. The cRMP (version 6.0, dated 25 October 2022) applicable at the end of

the reporting interval, was updated to reflect this change. Characterisation of this risk is provided in Section 16.4, Characterisation of Risks.

Methods

The Company global safety database was searched for medically confirmed and medically unconfirmed cases received during this reporting period and cumulatively. Since VTE is now an important identified risk, the Company has revised the strategy to focus on the SMQ "Embolic and thrombotic events, venous (narrow)". The SMQ Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous (narrow), is no longer included in the search criteria provided in Appendix 5.

Results/Discussion

During this reporting period, a total of 104 (77 medically confirmed and 27 medically unconfirmed) initial, primary dose cases reporting VTE were retrieved. There were 93 serious and 11 nonserious cases which reported a total of 142 EOI (129 serious, 13 nonserious).

During this reporting period, a total of 16 (13 medically confirmed and 3 medically unconfirmed) initial cases reported as booster were identified. There were 10 serious and 6 nonserious cases which reported a total of 18 EOI (12 serious, 6 nonserious). Of these cases, 11 were homologous and 5 were heterologous.

Post-marketing Sources (Including Spontaneous and Solicited) Cases

Primary Dose

During this reporting period, a total of 67 (40 medically confirmed and 27 medically unconfirmed) post-marketing, initial, primary dose cases reporting VTE were retrieved. There were 65 serious and 2 nonserious cases which reported a total of 101 EOI (99 serious, 2 nonserious).

Cumulatively, 2,194 (1,499 medically confirmed and 695 medically unconfirmed) post-marketing, primary dose cases reporting VTE were retrieved. There were 2,113 serious and 81 nonserious cases which reported a total of 2,842 EOI (2,732 serious, 110 nonserious).

An overview of these cases is presented in Table 51 below.

Table 51: Characteristics of Post-marketing Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Venous Thromboembolism

Case Characteristics		Number of Cases Received During the Interval Reporting Period=67	Number of Cases Received Cumulatively=2,194[a]
Sex	Male	31	1,092
	Female	29	1,034
	NR	7	68

Table 51: 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 Period=67	Number of Cases Received Cumulatively=2,194[a]
Age (Years)[b]	18 to 35	11	276
Minimum: 18	36 to 50	20	591
Maximum: 83	51 to 64	14	729
Mean: 50.9	≥65	15	487
Median: 49.5	Adult	1	16
	NR	6	91
Source	Spontaneous	64	2,170
	Clinical study (noninterventional, solicited)	3	24
Country/Territory[c]	United States	45	1,518
	Germany	7	225
	Canada	3	3
	Greece	3	19
	South Africa	3	19
Event Characteristics		**Number of Events=101**	**Number of Events=2,842**
Seriousness (Event Level)[d]	Serious	99	2,732
	Nonserious	2	110
Outcome (Event Level)[d]	Not resolved	20	1,221
	Resolving	10	308
	Resolved	9	353
	Fatal	8	176
	Resolved with sequelae	3	28
	NR	51	756

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 period (25 August 2022 to 24 February 2023).

b: The median and mean age calculation were based on the current reporting period (25 August 2022 to 24 February 2023). Age group was presented for cases where age was not reported.

c: Countries/territories with frequency ≥3 were presented in decreasing order for the current reporting period (25 August 2022 to 24 February 2023).

d: Seriousness and outcome have been presented for the events of interest. A single case may report more than 1 EOI.

Of these 67 post-marketing, primary dose cases received, the most frequently reported countries/territories of origin (n≥3) were the US (n=45), Germany (n=7), and followed by Canada, Greece, and South Africa (n=3 each). These cases concerned 31 males, 29 females, and 7 did not report sex. The age range was from 18 to 83 years.

The frequency distribution of the MedDRA PTs of interest reported is presented in Table 52 below.

Table 52: Frequency Distribution of MedDRA PTs 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 Period[a]		Number of Events Reported Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
Deep vein thrombosis	23	0	807	1
Pulmonary embolism	22	0	961	1
Cerebral venous sinus thrombosis	10	0	151	0

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: The MedDRA PTs of interest with a frequency ≥10 have been presented and sorted by decreasing order for the reporting period (25 August 2022 to 24 February 2023). 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 period (25 August 2022 to 24 February 2023).

The EOI reported at a frequency ≥10 included deep vein thrombosis (n=23), pulmonary embolism (n=22), and cerebral venous sinus thrombosis (n=10). The mean and median TTO were 161.1 and 61.0 days, respectively, and the range was from 0 to 653 days. Of the 101 EOI, outcomes were reported for 50 and are as follows: not resolved (n=20), resolving (n=10), resolved (n=9), fatal (n=8), and resolved with sequelae (n=3).

Booster Dose

During this reporting period, a total of 10 (7 medically confirmed and 3 medically unconfirmed) initial cases reported as booster were identified. All cases were serious and reported a total of 12 serious EOI. Of these cases, 7 were homologous and 3 were heterologous.

Cumulatively, 70 (42 medically confirmed and 28 medically unconfirmed) cases reported as booster were identified. All cases were serious and reported a total of 83 serious EOI. Of these cases, 42 were homologous and 28 were heterologous.

An overview of these cases is presented in Table 53 below.

Table 53: 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 Interval Reporting Period=10	Number of Cases Received Cumulatively=70[a]
Sex	Male	5	41
	Female	3	27
	NR	2	2
Age (Years)[b]	18 to 35	1	7
Minimum: 33	36 to 50	3	22
Maximum: 85	51 to 64	2	12
Mean: 53.6	≥65	2	23

Table 53: 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 Interval Reporting Period=10	Number of Cases Received Cumulatively=70[a]
Median: 52.0	NR	2	5
Source	Spontaneous	10	66
Country/Territory	United States	7	46
	France	1	1
	Germany	1	6
	South Africa	1	2
Classification	Homologous	7	42
	Heterologous	3	28
Event Characteristics		**Number of Events=12**	**Number of Events=83**
Seriousness (Event Level)[c]	Serious	12	83
Outcome (Event Level)[c]	Resolved	3	19
	Not resolved	1	19
	NR	8	28

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 period (25 August 2022 to 24 February 2023).
b: The median and mean age calculations were based on the current reporting period (25 August 2022 to 24 February 2023).
c: Seriousness and outcome have been presented for the events of interest. A single case may report more than 1 EOI.

Of these 10 post-marketing cases reported as booster, reported countries/territories of origin were the US (n=7), and followed by France, Germany, and South Africa (n=1 each). These cases concerned 5 males, 3 females, and 2 did not report sex. The age range was from 33 to 85 years.

The frequency distribution of the MedDRA PTs of interest reported in post-marketing cases reported as booster is presented in Table 54 below.

Table 54: Frequency Distribution of MedDRA PTs in Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Venous Thromboembolism

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
Deep vein thrombosis	5	0	31	0
Pulmonary embolism	2	0	22	0
Pulmonary thrombosis	2	0	10	0
Central venous catheterisation	1	0	2	0

Table 54: Frequency Distribution of MedDRA PTs in Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Venous Thromboembolism

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
Cerebral venous sinus thrombosis	1	0	4	0
Retinal vein occlusion	1	0	2	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 period (25 August 2022 to 24 February 2023). 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 period (25 August 2022 to 24 February 2023).

The EOI included deep vein thrombosis (n=5), and pulmonary embolism and pulmonary thrombosis (n=2 each), and central venous catheterisation, cerebral venous sinus thrombosis, and retinal vein occlusion (n=1 each). The mean and median TTO were 337.7 and 357.5 days, respectively, and the range was from 29 to 493 days. Of the 12 EOI, outcomes were reported for 4 and are as follows: resolved (n=3) and not resolved (n=1).

Clinical Trial Cases

During this reporting period, a total of 43 clinical cases (37 primary dose and 6 booster) were retrieved from Janssen Sponsored and Janssen Supported Clinical Studies.

Janssen Sponsored Clinical Studies

During this reporting period, a total of 36 primary dose cases reporting VTE were retrieved from Janssen Sponsored Clinical Studies. Of the 36 cases, 19 were from VAC31518COV3001, 16 from VAC31518COV3009, and 1 from VAC31518COV1001. These 36 cases reported 40 EOI (29 serious, 11 nonserious). Of these 36 cases, the most frequently reported countries/territories of origin (n≥3) were the US (n=19), and followed by Belgium, South Africa, Spain, and the UK (n=3 each). These cases concerned 22 males and 14 females. The age range was from 26 to 89 years.

The EOI reported at a frequency ≥2 included pulmonary embolism (n=17), deep vein thrombosis (n=12), and superficial vein thrombosis and venous thrombosis limb (n=2 each). The mean and median TTO were 520.0 and 549.0 days, respectively, and the range was from 57 to 760 days. The reported outcomes of the EOI are as follows: resolved (n=16), resolving (n=12), not resolved (n=8), and resolved with sequelae (n=3), and fatal (n=1).

During this reporting period, a total of 6 cases reported as booster were retrieved from Janssen Sponsored Clinical Studies.

Of the 6 cases, 3 each were reported from VAC31518COV3009 and VAC31518COV3001. These 6 cases reported 6 nonserious EOI. The reported countries/territories of origin were Brazil (n=2), and followed by Argentina, Belgium, the UK, and the US (n=1 each). These cases concerned 3 males and females. The age range was from 55 to 78 years.

The most frequently reported EOI (n ≥4) included deep vein thrombosis. The mean and median TTO were 402.3 and 415.5 days, respectively, and the range was from 174 to 612 days. The reported outcomes of the EOI are as follows: resolved (n=4), and not resolved and resolving (n=1 each).

Janssen Supported Clinical Studies Cases

During this reporting period, 1 primary dose cases reporting VTE was retrieved from a Janssen Supported Clinical Study. This case was reported from [redacted] and concerned a male of unspecified age from [redacted] who experienced a serious EOI of pulmonary embolism. The TTO was 61 days, and the reported outcome was resolving.

During this reporting period, no cases reported as booster were retrieved from Janssen Supported Clinical Studies.

Literature ICSR

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

Line Listings

Death: During the current reporting period (25 August 2022 to 24 February 2023), a total of 9 fatal cases were retrieved. Of these cases, 7 reported a 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 7.27, Death.

Booster: A cumulative CIOMS II LL of cases reported as booster is presented in Appendix 7.14.2.

Discussion

Since VTE is now an important identified risk, the change in strategy has resulted in reduced number of cases retrieved for both interval and cumulative periods.

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.

16.3.2. New Information on Important Potential Risks

16.3.2.1. Vaccine-Associated Enhanced Disease Including Vaccine-Associated Enhanced Respiratory Disease

Introduction

According to the cRMP (version 5.0; dated 24 May 2022), vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD), is an important potential risk associated with the use of Ad26.COV2.S. Characterisation of this risk is provided in Section 16.4, Characterisation of Risks.

Methods

The Company global safety database was searched for medically confirmed and medically unconfirmed cases received during this reporting period and cumulatively, which coded to the search criteria provided in Appendix 5.

Results/Discussion

Primary Dose

There were no initial, primary dose cases retrieved from the search of the Company global safety database during this reporting period.

Cumulatively, 1 medically confirmed, post-marketing, primary dose case reporting VAED, including VAERD was retrieved. This case reported 1 serious EOI of VAED, 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 period. 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 period.

Line Listings

Death: During the current reporting period (25 August 2022 to 24 February 2023), no fatal cases were retrieved.

Conclusion

Based on the evaluation of the cases, and review of safety from other sources, no new information was received on the topic of VAED, including VAERD.

16.3.2.2. Immune Thrombocytopenia

Introduction

According to the cRMP (version 5.0; dated 24 May 2022), ITP is an important potential risk associated with the use of Ad26.COV2.S. In the EU RMP (version 4.2, dated 12 July 2022), this risk is characterised as "Thrombocytopenia, including ITP" and is listed as an important identified risk. Characterisation of this risk is provided in Section 16.4, Characterisation of Risks.

Methods

The Company global safety database was searched for medically confirmed and medically unconfirmed cases received during this reporting period and cumulatively which coded to the search criteria provided in Appendix 5.

The case definition for this topic is described within: as all cases that were retrieved from the database were individually reviewed and all cases meeting criteria for aggregate presentation were those that reported an EOI within the risk window of 42 days (or those where risk window was not reported), an identifiable patient with evidence of thrombocytopenia. All cases were reviewed for evidence of thrombocytopenia per the interim BC case definition v 10.16.3 for thrombocytopenia (Brighton Collaboration 2021a). It should be noted that there is no BC criteria for immune thrombocytopenia. Cases were then further screened using a case definition modified from the American Society of Hematology (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' (Table 55).

Table 55: Summary of ASH Case Definition for Immune Thrombocytopenia

	Platelet	**Treatment**	**Anti-platelet Autoantibody Test**	**Causes of Thrombocytopenia (Clinical Manifestations)**
Confirmed	A platelet count $<100x10^9$/L, with the exclusion of other causes of thrombocytopenia AND a low platelet count nadir ($<20x10^9$/L)	AND a platelet count response to therapy (corticosteroids, IVIG, or treatment of the underlying secondary cause)	AND a positive anti-platelet autoantibody test	(Exclusion of other causes of thrombocytopenia)
Likely	A platelet count $<100x10^9$/L; OR a low platelet count nadir ($<20x10^9$/L)	OR a platelet count response to therapy (corticosteroids, IVIG, or treatment of the underlying secondary cause)	OR a positive anti-platelet autoantibody test	AND with the exclusion of other causes of thrombocytopenia

Table 55: Summary of ASH Case Definition for Immune Thrombocytopenia

	Platelet	Treatment	Anti-platelet Autoantibody Test	Causes of Thrombocytopenia (Clinical Manifestations)
Suspect	-	-	-	Reported thrombocytopenia without a reported underlying or associated cause
Excluded	-	-	-	No thrombocytopenia secondary to other disease (eg, tumour)

Key: ASH=American Society of Hematology; IVIG=Intravenous Immunoglobulin

Results/Discussion

During this reporting period, a total of 84 (71 medically confirmed and 13 medically unconfirmed) initial, primary dose cases reporting thrombocytopenia were retrieved. There were 44 serious and 40 nonserious cases which reported a total of 90 EOI (43 serious, 47 nonserious).

During this reporting period, a total of 15 medically confirmed (no medically unconfirmed) initial cases reported as booster were identified. There were 3 serious and 12 nonserious cases which reported a total of 15 EOI (3 serious, 12 nonserious). Of these cases, 4 was heterologous and 11 were homologous.

Post-marketing Sources (Including Spontaneous and Solicited) Cases

Primary Dose

During this reporting period, a total of 39 (26 medically confirmed and 13 medically unconfirmed) post-marketing, initial, primary dose cases reporting thrombocytopenia were retrieved. All cases were serious and included a total of 44 EOI (40 serious; 4 nonserious). Out of these 39 cases, 20 cases were assessed as ITP cases per ASH case definition.

Cumulatively, 841 (610 medically confirmed and 231 medically unconfirmed) post-marketing, primary dose cases reporting thrombocytopenia were retrieved. There were 722 serious and 119 nonserious cases which reported a total of 987 EOI (836 serious, 151 nonserious). Out of 841 cases, 421 cases were assessed as ITP cases per ASH case definition.

An overview of these cases is presented in Table 56 below.

Table 56: Characteristics of Post-marketing Primary Dose Cases Involving the Use of Ad26.COV2.S and Assessed as Immune Thrombocytopenia

Case Characteristics		Number of Cases Received During the Interval Reporting Period=20	Number of Cases Received Cumulatively=421[a]
Sex	Female	10	202
	Male	8	214

Table 56: Characteristics of Post-marketing Primary Dose Cases Involving the Use of Ad26.COV2.S and Assessed as Immune Thrombocytopenia

Case Characteristics		Number of Cases Received During the Interval Reporting Period=20	Number of Cases Received Cumulatively=421[a]
	NR	2	5
Age (Years)[b] **Minimum: 40** **Maximum: 83** **Mean: 61.7** **Median: 65**	36 to 50 51 to 64 ≥65 NR	5 4 9 2	154 121 76 9
Source	Spontaneous	20	417
Country/Territory	United States	13	202
	Germany	3	41
	France	1	16
	Italy	1	12
	Portugal	1	3
Event Characteristics		**Number of Events=23**	**Number of Events=485**
Seriousness (Event Level)[c]	Serious	20	366
	Nonserious	3	119
Outcome (Event Level)[c]	Not resolved	10	153
	Resolved with sequelae	1	6
	Resolved	1	83
	NR	11	181

Key: EOI=Event of Interest; NR=Not Reported

a: For the cumulative column, the counts were presented in decreasing order based on the current reporting period (25 August 2022 to 24 February 2023).

b: The median and mean age calculations were based on the current reporting period (25 August 2022 to 24 February 2023).

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

Of these 20 cases received, the most frequently reported countries/territories of origin were the US (n=13), Germany (n=3), and followed by France and Italy (n=1 each). These cases concerned 8 males, 10 females, and 2 cases who did not report sex. The age range was from 40 to 83 year.

The frequency distribution of the MedDRA PTs of interest reported is presented in Table 57 below.

Table 57: Frequency Distribution of MedDRA PTs of Interest in Post-marketing Primary Dose Cases Assessed as Immune Thrombocytopenia With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
Platelet count decreased	8	3	119	41
Thrombocytopenia	7	0	143	0
Immune thrombocytopenia	5	0	82	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 period (25 August 2022 to 24 February 2023). 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 period (25 August 2022 to 24 February 2023).

The EOI included platelet count decreased (n=11), thrombocytopenia (n=7), immune thrombocytopenia (n=5). The mean and median TTO were 181.7 and 55 days, respectively, and the range was from 0 to 611 days. Of the 23 EOI, outcomes were reported for 12 and are as follows: not resolved (n=10), resolved with sequelae (n=1), and resolved (n=1).

Booster Dose

During this reporting period, 3 medically confirmed (no medically unconfirmed) initial cases reported as booster were identified. These 3 serious cases reported a total of 3 serious EOI. Out of these 3 cases, 1 case was assessed as ITP per ASH case definition. This post-marketing, heterologous case concerned a 64-year-old male from [redacted] who experienced a serious EOI of immune thrombocytopenia. The TTO was not reported, and outcome was reported as resolved.

Cumulatively, 23 (13 medically confirmed and 10 medically unconfirmed) cases reported as booster were identified. There were 20 serious and 3 nonserious cases which reported a total of 24 EOI (15 serious, 9 nonserious). Of these cases, 11 were heterologous and 12 were homologous. Out of 23 cases, 17 cases were assessed as ITP cases per ASH case definition.

Clinical Trial Cases

During this reporting period, a total of 57 clinical cases (45 primary and 12 booster) were retrieved from Janssen Sponsored Clinical Studies. No cases were retrieved from Janssen Supported Clinical Studies.

Janssen Sponsored Clinical Studies

During this reporting period, a total of 45 primary dose cases reporting thrombocytopenia were retrieved from Janssen Sponsored Clinical Studies. Of the 45 cases, 37 were reported from VAC31518COV3001, 5 from VAC31518COV3003, 2 from VAC31518COV3009, and 1 from VAC18193RSV2008. These 45 cases reported 46 EOI (43 nonserious; 3 serious). Of these 45 cases, the most frequently reported countries/territories of origin (n≥3) were the US (n=28),

Brazil (n=8), and Colombia (n=3). These cases concerned 34 males and 11 females. The age range was from 21 to 74 years.

The EOI included thrombocytopenia (n=40), platelet count decreased (n=5), and thrombosis with thrombocytopenia syndrome (n=1). The mean and median TTO were 354 and 350 days, respectively, and the range was from 0 to 713 days. Of the 46 EOI, outcomes were reported for 42 and are as follows: resolved (n=32), resolving (n=6), and not resolved (n=4).

During this reporting period, a total of 12 cases reported as booster were retrieved from Janssen Sponsored Clinical Studies. Nine were reported from VAC31518COV3001, 2 from VAC31518COV3009, and 1 from VAC31518COV3005. These 12 cases reported 12 nonserious EOI. Of these 12 cases, the countries/territories of origin were the US (n=6), Brazil (n=3), Colombia (n=2), and Chile (n=1). These cases concerned 9 males and 3 females. The age range was from 55 to 73 years.

The EOI included thrombocytopenia (n=11) and platelet count decreased (n=1). The mean and median TTO were 71.1 and 18 days, respectively, and the range was from 0 to 531 days. The outcomes were reported as resolved (n=10) and resolving (n=2).

Janssen Supported Clinical Studies Cases

During this reporting period, there were no cases retrieved from Janssen Supported Clinical Studies.

Literature ICSR

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

Line Listings

Death: During the current reporting period (25 August 2022 to 24 February 2023), a total of 3 fatal cases were retrieved. Of these cases, 1 reported a fatal EOI.

A CIOMS II LL of the fatal case is presented in Appendix 7.15.1. Additional information on the fatal case can also be found in Appendix 7.27, 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 from other sources, the information is consistent with what is currently known about immune thrombocytopenia.

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 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, PRAC indicated that,

"*The section 'Update on special patient populations', i.e. pregnancy/breastfeeding; Use in immunocompromised patients; Use in patients with autoimmune or inflammatory disorders; Use in frail patients with comorbidities (e.g., chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders should only be included and discussed in the PSUR if the reporting pattern changes and/or there is a safety issue/signal*".

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 covered in Section 16.3.5.1, Use During Pregnancy above.

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, 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

In alignment with the presentation of the other missing information topics, information on long-term safety 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 AESI and vaccination with the Ad26.COV2.S. Information on these analyses are found in Appendices 6.3.

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, PRAC endorsed the discontinuation of presentation of the following separate AESI within the current and future PBRERs: acute aseptic arthritis, acute kidney failure, acute renal failure; convulsions, disseminated intravascular coagulation, sensorineural hearing loss, and transverse myelitis. These topics will not be discussed within this PBRER or in future PBRERs.

16.3.6.1. Cardiac Disorders

16.3.6.1.1. Cardiac Inflammatory disorder (Including Myocarditis and Pericarditis)

On 14 February 2023 a signal was identified for cardiac inflammatory disease (including myocarditis and pericarditis) with the use Ad26.COV2.S based on a request from the US FDA to perform a review of the topic.

Additional information on the cumulative analysis of myocarditis/pericarditis can be found in Section 14, Late-Breaking Information and in Appendix 7.2.

16.3.6.1.2. Cardiomyopathy

Introduction

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

Methods

The Company global safety database was searched for medically confirmed and medically unconfirmed cases received during this reporting period and cumulatively, which coded to the search criteria provided in Appendix 5.

An O/E analysis has been performed and information is presented in the O/E Analysis subsection below.

Results/Discussion

During this reporting period, a total of 4 (3 medically confirmed and 1 medically unconfirmed) initial, primary dose cases reporting cardiomyopathy were retrieved. All cases were serious and reported a total of 5 serious EOI.

During this reporting period, 1 medically unconfirmed, initial case reported as booster was identified. This serious case was heterologous and reported 1 serious EOI.

Post-marketing Sources (Including Spontaneous and Solicited) Cases

Primary Dose

During this reporting period, a total of 2 (1 medically confirmed and 1 medically unconfirmed) post-marketing, initial, primary dose cases reporting cardiomyopathy were retrieved. Both cases were serious and reported a total of 3 serious EOI.

Cumulatively, 73 (47 medically confirmed and 26 medically unconfirmed) post-marketing, primary dose cases reporting cardiomyopathy were retrieved. All cases were serious and reported a total of 82 EOI (79 serious, 3 nonserious).

Of these 2 post-marketing, primary dose cases retrieved, the only reported country/territory of origin was the US. These cases concerned 1 female and 1 male, aged 62 and 22 years, respectively.

The EOI included ejection fraction decreased, hypertrophic cardiomyopathy, and ischaemic cardiomyopathy (n=1 each). The mean and median TTO were 208.3 and 307.0 days, respectively, and the range was from 11 to 307. The reported outcomes of the EOI were resolved (n=2) and not resolved (n=1).

Booster Dose

During this reporting period, 1 medically unconfirmed, post-marketing, initial case reported as booster was identified. This heterologous case concerned a 43-year-old male from [redacted] who experienced a serious EOI of cardiomyopathy. The TTO was 143 days, and the outcome was reported as not resolved.

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 EOI. Of these cases, 4 were heterologous and 1 was homologous.

Clinical Trial Cases

During this reporting period, a total of 2 clinical cases (both primary dose and no booster) were retrieved from Janssen Sponsored Clinical Studies and no cases were retrieved from Janssen Supported Clinical Studies.

Janssen Sponsored Clinical Studies

During this reporting period, a total of 2 primary dose cases reporting cardiomyopathy were retrieved from Janssen Sponsored Clinical Studies. Of the 2 cases, 1 each was reported from VAC31518COV3009 and VAC31518COV3001. These 2 cases reported 2 serious EOI. Of these 2 cases, the only reported country/territory of origin was [redacted] These cases concerned 1 female and 1 male, aged 78 and 66 years, respectively.

The EOI included cardiac amyloidosis and ischaemic cardiomyopathy (n=1 each). The TTO was only reported for 1 case as 479 days. The reported outcomes were not resolved and resolving (n=1 each).

During this reporting period, no cases reported as booster were retrieved from Janssen Sponsored Clinical Studies.

Literature ICSR

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

Line Listings

Death: During the current reporting period (25 August 2022 to 24 February 2023), 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 the cardiomyopathy. Results of the restricted O/E and sensitivity analysis are presented in Table 58 below.

Table 58: Cardiomyopathy: Restricted O/E and Sensitivity Analysis Results (Cumulative Through 24 February 2023)

	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	9.00	0.69	(0.32, 1.31)	2.33	(1.07, 4.42)
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)

Table 58: Cardiomyopathy: Restricted O/E and Sensitivity Analysis Results (Cumulative Through 24 February 2023)

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)

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.

Results of the US and EU O/E analysis (both broad and restricted, where applicable) are provided in Appendix 6.2, this includes cumulative exposure, expected counts, and background incidence rates.

Discussion

Of the 5 primary and booster dose cases received in this interval, there was an approximately even distribution of males and females. Ages reported ranged from 22 to 78, with 3 cases concerning patients 62 years and older. Four of the cases reported concurrent conditions that confound assessment, and these concurrent conditions included hypertension, blood cholesterol increased, hyperlipidaemia, cardiac conditions (atrial flutter, atrial fibrillation, coronary artery disease, congestive cardiac failure, myocardial infarction, ischaemic cardiomyopathy), carcinoma, drug abuse, and nicotine dependence. TTO ranged from 11 days to 479 days, with 3 of the cases reporting TTO of 143 days or more. 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 cardiopathy 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 cardiopathy as an AESI.

16.3.6.1.3. Coronary Artery Disease (Including Acute Myocardial Infarction)

Introduction

Coronary artery disease (CAD), including acute myocardial infarction (MI) is listed as an AESI in the cRMP, EU RMP, and the US PVP.

Methods

The Company global safety database was searched for medically confirmed and medically unconfirmed cases received during this reporting period and cumulatively, which coded to the search criteria provided in Appendix 5.

An O/E analysis has been performed and information is presented in the O/E Analysis subsection below.

Results/Discussion

During this reporting period, a total of 102 (74 medically confirmed and 28 medically unconfirmed) initial, primary dose cases reporting CAD, including acute MI were retrieved. There were 99 serious and 3 nonserious cases, which reported a total of 116 EOI (113 serious, 3 nonserious).

During this reporting period, a total of 16 (7 medically confirmed and 9 medically unconfirmed) initial cases reported as booster were identified. All cases were serious and reported a total of 20 serious EOI. Of these cases, 11 were homologous, and 5 were heterologous.

Post-marketing Sources (Including Spontaneous and Solicited) Cases

Primary Dose

During this reporting period, a total of 49 (21 medically confirmed and 28 medically unconfirmed) post-marketing, initial, primary dose cases reporting CAD, including acute MI were retrieved. There were 47 serious and 2 nonserious cases which reported a total of 60 EOI (58 serious, 2 nonserious).

Cumulatively, 774 (371 medically confirmed and 403 medically unconfirmed) post-marketing, primary dose cases reporting CAD, including acute MI were retrieved. There were 768 serious and 6 nonserious cases which reported a total of 964 EOI (951 serious, 13 nonserious).

An overview of these cases is presented in Table 59 below.

Table 59: Characteristics of Post-marketing Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Coronary Artery Disease, Including Acute Myocardial Infarction

Case Characteristics		Number of Cases Received During the Interval Reporting Period=49	Number of Cases Received Cumulatively=774[a]
Sex	Male	29	462
	Female	15	279
	NR	5	33
Age (Years)[b]	18 to 35	9	108
	36 to 50	6	154

Table 59: Characteristics of Post-marketing Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Coronary Artery Disease, Including Acute Myocardial Infarction

Case Characteristics		Number of Cases Received During the Interval Reporting Period=49	Number of Cases Received Cumulatively=774[a]
Minimum: 24 **Maximum: 79** **Mean: 52.1** **Median: 53.0**	51 to 64	13	257
	≥65	10	192
	NR	11	57
Source	Spontaneous	46	752
	Clinical study (noninterventional, solicited)	3	19
Country/Territory[c]	United States	26	439
	Germany	8	123
	Greece	3	11
	Philippines	2	20
Event Characteristics		**Number of Events=60**	**Number of Events=964**
Seriousness (Event Level)[d]	Serious	58	951
	Nonserious	2	13
Outcome (Event Level)[d]	Not resolved	10	259
	Resolved	8	181
	Fatal	7	138
	Resolved with sequelae	5	42
	Resolving	2	91
	NR	28	253

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 period (25 August 2022 to 24 February 2023).

b: The median and mean age calculation were based on the current reporting period (25 August 2022 to 24 February 2023).

c: Countries/territories with frequency ≥2 were presented in decreasing order for the current reporting period (25 August 2022 to 24 February 2023).

d: Seriousness and outcome have been presented for the events of interest. A single case may report more than 1 EOI.

Of these 49 cases received, the most frequently reported countries/territories of origin (n≥2) were the US (n=26), Germany (n=8), Greece (n=3) and the Philippines (n=2). These cases concerned 29 males, 15 females, and 5 did not report sex. The age range was from 24 to 79 years.

The frequency distribution of the MedDRA PTs of interest reported is presented in Table 60 below.

Table 60: Frequency Distribution of MedDRA PTs of Interest in Post-marketing Primary Dose Cases Reporting Coronary Artery Disease, Including Acute Myocardial Infarction With the Use of Ad26.COV2.S

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
Myocardial infarction	18	0	289	0
Acute myocardial infarction	13	0	150	0
Angina pectoris	9	2	195	2
Coronary artery disease	3	0	26	2
Troponin increased	3	0	84	6

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: The MedDRA PTs of interest with a frequency ≥3 have been presented and sorted by decreasing order for the reporting period (25 August 2022 to 24 February 2023). 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 period (25 August 2022 to 24 February 2023).

The EOI reported (n≥3) included myocardial infarction (n=18), acute myocardial infarction (n=13), angina pectoris (n=11), and coronary artery disease and troponin increased (n=3 each). The mean and median TTO were 151.0 and 88.0 days, respectively, and the range was from 0 to 578 days. Of the 60 EOI, outcomes were reported for 32 and are as follows: not resolved (n=10), resolved (n=8), fatal (n=7), resolved with sequelae (n=5), and resolving (n=2).

Booster Dose

During this reporting period, a total of 14 (5 medically confirmed and 9 medically unconfirmed) initial cases reported as booster were identified. All cases were serious and reported a total of 18 serious EOI. Of these cases, 10 were homologous and 4 were heterologous.

Cumulatively, 58 (19 medically confirmed and 39 medically unconfirmed) cases reported as booster were identified. All cases were serious and reported a total of 69 serious EOI. Of these cases, 31 were heterologous and 27 were homologous.

An overview of these cases is presented in Table 61 below.

Table 61: Characteristics of Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Coronary Artery Disease, Including Acute Myocardial Infarction

Case Characteristics		Number of Cases Received During the Interval Reporting Period=14	Number of Cases Received Cumulatively=58[a]
Sex	Male	8	35
	Female	5	19
	NR	1	4

Table 61: Characteristics of Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Coronary Artery Disease, Including Acute Myocardial Infarction

Case Characteristics		Number of Cases Received During the Interval Reporting Period=14	Number of Cases Received Cumulatively=58[a]
Age (Years)[b]	18 to 35	1	4
Minimum: 35	36 to 50	5	13
Maximum: 81	51 to 64	4	18
Mean: 52.7	≥65	1	10
Median: 50.0	NR	3	10
Source	Spontaneous	14	57
Country/Territory	United States	9	27
	Germany	5	12
Classification	Homologous	10	27
	Heterologous	4	31
Event Characteristics		**Number of Events=18**	**Number of Events=69**
Seriousness (Event Level)[c]	Serious	18	69
Outcome (Event Level)[c]	Resolved with sequelae	4	4
	Fatal	2	11
	Not resolved	1	12
	Resolved	1	12
	NR	10	26

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 period (25 August 2022 to 24 February 2023).

b: The median and mean age calculations were based on the current reporting period (25 August 2022 to 24 February 2023).

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

Of these 14 post-marketing cases reported as booster, the countries/territories of origin were the US (n=9) and Germany (n=5). These cases concerned 8 males, 5 females, and 1 did not report sex. The age range was from 35 to 81 years.

The frequency distribution of the MedDRA PTs of interest reported in post-marketing cases reported as booster is presented in Table 62 below.

Table 62: Frequency Distribution of MedDRA PTs of Interest in Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Coronary Artery Disease, Including Acute Myocardial Infarction

MedDRA PTs	Number of Events Reported During the Interval Reporting Period[a]		Number of Events Reported Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
Myocardial infarction	8	0	24	0
Angina pectoris	4	0	21	0
Acute myocardial infarction	2	0	9	0
Coronary artery disease	2	0	4	0

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 current reporting period (25 August 2022 to 24 February 2023). 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 period (25 August 2022 to 24 February 2023).

The EOI reported (n≥2) included myocardial infarction (n=8), angina pectoris (n=4), and acute myocardial infarction and coronary artery disease (n=2 each). The mean and median TTO were 214.7 and 251.0 days, respectively, and the range was from 0 to 429 days. Of the 18 EOI, outcomes were reported for 8 and are as follows: resolved with sequelae (n=4), fatal (n=2), and not resolved and resolved (n=1 each).

Clinical Trial Cases

During this reporting period, a total of 55 clinical cases (53 primary dose and 2 booster) were retrieved from Janssen Sponsored and Janssen Supported Clinical Studies.

Janssen Sponsored Clinical Studies

During this reporting period, a total of 52 primary dose cases reporting CAD, including acute MI were retrieved from Janssen Sponsored Clinical Studies. Of the 52 cases, 29 were reported from VAC31518COV3001, 22 from VAC31518COV3009, and 1 from VAC31518COV2008. These 52 cases reported 55 EOI (54 serious, 1 nonserious). Of these 52 cases, the most frequently reported countries/territories of origin (n≥5) were the US (n=16), Brazil (n=8), and followed by Belgium and Columbia (n=5 each). These cases concerned 38 males and 14 females. The age range was from 44 to 94 years.

The EOI reported (n≥5) included acute myocardial infarction (n=18), coronary artery disease (n=14), and angina unstable and myocardial infarction (n=5 each). The mean and median TTO were 539.0 and 538.5 days, respectively, and the range was from 186 to 752 days. The reported outcomes were as follows: resolved (n=28), resolving (n=14), fatal and not resolved (n=5 each), and resolved with sequelae (n=3).

During this reporting period, a total of 2 cases reporting booster doses were retrieved from a Janssen Sponsored Clinical Study. Both cases were reported from VAC31518COV3001. These

2 cases reported 2 serious EOI. The countries/territories of origin reported were [redacted] and [redacted] (n=1 each). Both cases concerned males, aged 62 and 69 years, respectively.

The EOI included acute coronary syndrome and acute myocardial infarction (n=1 each). The reported TTO were 114 and 192 days. The reported outcomes were as follows: resolving and not resolved (n=1 each).

Janssen Supported Clinical Studies Cases

During this reporting period, 1 primary dose case reporting CAD, including acute MI was retrieved from a Janssen Supported Clinical Study. This case was reported from [redacted] and concerned a 72-year-old female from [redacted] who experienced a serious EOI of acute myocardial infarction. The reported TTO was 265 days, and the outcome was reported as resolving.

During this reporting period, no cases reported as booster were retrieved from Janssen Supported Clinical Studies.

Literature ICSR

ICSR literature cases received during the current reporting period were reviewed, and no information was identified that would change the information known about CAD, including acute MI.

Line Listings

Death: During the current reporting period (25 August 2022 to 24 February 2023), a total of 16 fatal cases were retrieved. Of these cases, 14 reported a 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 7.27, Death.

Booster: A cumulative CIOMS II LL of cases reported as booster is presented in Appendix 7.22.2.

O/E Analysis Results

Appendix 6.1 contains the methods used to calculate and perform the O/E analyses for the CAD, including acute MI.

Since the previous PBRER DLP (24 August 2022), the broad O/E ratio has remained <1 in the US and EU for both age groups. A restricted O/E analysis with sensitivity analysis was not required.

Results of the US and EU O/E analysis (broad) are provided in Appendix 6.2, this includes cumulative exposure, expected counts, and background incidence rates.

Conclusion

Based on the evaluation of the cases, and review of safety from other sources, the information retrieved during the reporting period remains consistent with previous observations regarding CAD, including acute MI following Ad26.COV2.S. No safety concern has been identified and based on the overall reporting of cases within the expected range, the Company proposes to monitor CAD, including acute MI through regular pharmacovigilance activities.

16.3.6.2. Nervous System Disorders

16.3.6.2.1. Encephalitis (Including Acute Disseminated Encephalomyelitis 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.

Methods

The Company global safety database was searched for medically confirmed and medically unconfirmed cases received during this reporting period and cumulatively, which coded to the search criteria provided in Appendix 5.

An O/E analysis has been performed and information is presented in the O/E Analysis subsection below.

Results/Discussion

During this reporting period, a total of 5 (2 medically confirmed and 3 medically unconfirmed) initial, primary dose cases reporting encephalitis, including ADEM and meningoencephalitis, were identified. All 5 cases were serious and reported a total of 5 serious EOI.

During this reporting period, 1 medically confirmed, initial case reported as booster was identified. This serious case was homologous and reported 1 serious EOI.

Post-marketing Sources (Including Spontaneous and Solicited) Cases

Primary Dose

During this reporting period, a total of 4 (1 medically confirmed and 3 medically unconfirmed) post-marketing, initial, primary dose cases reporting encephalitis, including ADEM and meningoencephalitis were retrieved. All 4 cases were serious and reported a total of 4 serious EOI.

Cumulatively, 88 (59 medically confirmed and 29 medically unconfirmed) post-marketing, primary dose cases reporting encephalitis, including ADEM and meningoencephalitis were identified. All cases were serious and reported a total of 92 serious EOI.

In these 4 post-marketing primary dose cases received during this reporting period, the reported countries/territories of origin were the US (n=2), and followed by Denmark and South Africa (n=1 each). These cases concerned 3 females and 1 male. The age range was from 24 to 46 years.

The EOI included encephalitis autoimmune (n=2), and acute disseminated encephalomyelitis and encephalitis (n=1 each). Of the 4 cases, the TTO was reported only for 1 case as 5 days. Of the 4 EOI, outcomes were reported for 3 and are as follows: not resolved, resolved, and resolved with sequelae (n=1 each).

Booster Dose

During this reporting period, 1 medically confirmed, post-marketing, initial case reported as booster was identified. This homologous case concerned a 47-year-old male from [redacted] who experienced a serious EOI of encephalitis autoimmune. The TTO and outcome of the EOI were not reported.

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 period, 1 clinical case (primary dose and no booster) was retrieved from a Janssen Sponsored Clinical Study and no cases were retrieved from Janssen Supported Clinical Studies.

Janssen Sponsored Clinical Studies

During this reporting period, 1 primary dose case reporting encephalitis, including ADEM and meningoencephalitis, was retrieved from a Janssen Sponsored Clinical Study. It was confirmed that the patient was randomised to placebo group. The case is in the process of being updated and the change will be reflected in the next PBRER. This case was reported from VAC31518COV3009 and concerned a 75-year-old female from [redacted] who experienced a serious EOI of encephalitis autoimmune. The TTO was not reported, and the outcome was reported was resolving.

Literature ICSR

ICSR literature cases received during the current reporting period 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 period (25 August 2022 to 24 February 2023), 1 fatal case with no fatal EOI was retrieved.

A CIOMS II LL of the fatal case is presented in Appendix 7.23.1. Additional information on the fatal case can also be found in Appendix 7.27, 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 methods used to calculate and perform the O/E analyses for encephalitis, including ADEM and meningoencephalitis. Results of the restricted O/E and sensitivity analysis are presented in Table 63 below.

Table 63: Encephalitis, ADEM Alone: Restricted O/E and Sensitivity Analysis Results (Cumulative Through 24 February 2023)

		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	21.00	0.15	(0.09, 0.22)	2.52	(1.56, 3.86)
ADEM	**US**	18 to 59	7.65	0.61	(0.26, 1.22)	3.17	(1.34, 6.33)
	EU	18 to 59	5.00	0.35	(0.11, 0.81)	1.80	(0.58, 4.20)

Key: ADEM=Acute Disseminated Encephalomyelitis; CI=Confidence Interval; AESI=Adverse Event of Special Interest; EU=European Union; EOI=Event(s) of Interest; LB=Lower Bound; O/E=Observed Versus Expected; PE=Point Estimate; RP=Reporting Percentage; US=United States

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

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

Encephalitis

The US restricted sensitivity analysis showed an O/E ratio of >1 for the 18 to 59 age group only. This O/E ratio was statistically significant above 1 (lower bound of 95% confidence interval >1). The lower bound of the 95% confidence interval for the 18 to 59 age group was <1 in the previous interval. 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).

ADEM

The US restricted sensitivity analysis showed an O/E ratio of >1 for the 18 to 59 age group. This O/E ratio was statistically significant above 1 (lower bound of 95% confidence interval >1). The EU restricted sensitivity analysis showed an O/E ratio of >1 for the 18 to 59 age group. This O/E ratio was not statistically significant above 1 (lower bound of 95% confidence interval <1).

Results of the US and EU O/E analysis (both broad and restricted, where applicable) are provided in Appendix 6.2, this includes cumulative exposure, expected counts, and background incidence rates.

Conclusion

Based on the evaluation of the cases, and review of safety from other sources, the information retrieved during the reporting period 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 period and cumulatively, which coded to the search criteria provided in Appendix 5.

An O/E analysis has been performed and information is presented in the O/E Analysis subsection below.

Results/Discussion

During this reporting period, a total of 6 (3 medically confirmed and 3 medically unconfirmed) initial, primary dose cases reporting multiple sclerosis, including optic neuritis, were retrieved. All 6 cases were serious and reported a total of 6 serious EOI.

During this reporting period, a total of 3 (1 medically confirmed and 2 medically unconfirmed) initial cases reported as booster were identified. All 3 cases were serious and reported a total of 3 serious EOI reporting multiple sclerosis, including optic neuritis. Of these cases, 2 cases were heterologous and 1 was homologous.

Post-marketing Sources (Including Spontaneous and Solicited) Cases

Primary Dose

During this reporting period, a total of 5 (2 medically confirmed and 3 medically unconfirmed) post-marketing, initial, primary dose cases reporting multiple sclerosis, including optic neuritis, were retrieved. All 5 cases were serious and reported a total of 5 serious EOI.

Cumulatively, 72 (35 medically confirmed and 37 medically unconfirmed) post-marketing, primary dose cases reporting multiple sclerosis, including optic neuritis, were retrieved. All 72 cases were serious and reported a total of 74 serious EOI.

An overview of these cases is presented in Table 64 below.

Table 64: Characteristics of Post-marketing Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Multiple Sclerosis, Including Optic Neuritis

Case Characteristics		Number of Cases Received During the Interval Reporting Period=5	Number of Cases Received Cumulatively=72[a]
Sex	Female	2	38
	Male	2	30
	NR	1	4
Age (Years)[b]	18 to 35	1	19
Minimum: 33	36 to 50	2	30
Maximum: 62	51 to 64	1	13
Mean: 46	NR	1	6
Median: 44.5			
Source	Spontaneous	5	71
Country/Territory	United States	2	40
	Belgium	1	2
	Czech Republic	1	3
	Germany	1	10
Event Characteristics		**Number of Events=5**	**Number of Events=74**
Seriousness (Event Level)[c]	Serious	5	74
Outcome (Event Level)[c]	Resolved with sequelae	2	5
	Not resolved	1	46
	NR	2	13

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 period (25 August 2022 to 24 February 2023).
b: The median and mean age calculation were based on the current reporting period (25 August 2022 to 24 February 2023).
c: Seriousness and outcome have been presented for the EOI.

Of these 5 post-marketing primary dose cases received, the countries/territories of origin were the US (n=2), and followed by Belgium, Czech Republic, and Germany (n=1 each). These cases concerned 2 males, 2 females, and 1 did not report sex. The age range was from 33 to 62 years.

The frequency distribution of the MedDRA PTs of interest reported is presented in Table 65 below.

Table 65: 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 Period[a]		Number of Events Reported Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
Multiple sclerosis	2	0	35	0
Multiple sclerosis relapse	2	0	12	0
Optic neuritis	1	0	26	0

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: The MedDRA PTs of interest have been sorted by decreasing order for the reporting period (25 August 2022 to 24 February 2023).
b: For the cumulative column, the events were presented in decreasing order based on the event counts of the current reporting period (25 August 2022 to 24 February 2023).

The EOI included multiple sclerosis and multiple sclerosis relapse (n=2 each), and optic neuritis (n=1). The mean and median TTO were 98 and 101.5 days, respectively, and the range was from 25 to 164 days. Of the 5 EOI, outcomes were reported for 3 and are as follows: resolved with sequelae (n=2) and not resolved (n=1).

Booster Dose

During this reporting period, a total of 3 (1 medically confirmed and 2 medically unconfirmed) post-marketing, initial cases reported as booster were identified. All 3 cases were serious and reported a total of 3 serious EOI. Of these cases, 2 were heterologous and 1 was homologous.

Cumulatively, 8 (4 medically confirmed and 4 medically unconfirmed) post-marketing cases reported as booster were identified. All 8 cases were serious and reported a total of 10 serious EOI. Of these cases, 5 were heterologous and 3 were homologous.

Of the 3 initial post-marketing cases reported as booster, the countries/territories of origin were Germany (n=2) and Spain (n=1). These cases concerned 2 females and 1 male. The age range was from 25 to 71 years.

The EOI included leukoencephalopathy, optic neuritis, and relapsing-remitting multiple sclerosis (n=1 each). The mean and median TTO were 89.3 and 32 days, respectively, and the range was from 7 to 229 days. The outcomes were reported as not resolved (n=2) and resolved with sequelae (n=1).

Clinical Trial Cases

During this reporting period, a total of 1 clinical case (primary dose, no booster) was retrieved from a Janssen Sponsored Clinical Study and no cases were retrieved from Janssen Supported Clinical Studies.

Janssen Sponsored Clinical Studies

During this reporting period, 1 primary dose case reporting multiple sclerosis, including optic neuritis, was retrieved from a Janssen Sponsored Clinical Study. This case was reported from

[redacted] This case reported 1 serious EOI optic neuritis with a TTO of 5 days in a 26-year-old female from [redacted] The outcome was reported as resolved.

During this reporting period, no cases reported as booster were identified from Janssen Sponsored Clinical Studies.

Literature ICSR

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

Line Listings

Death: During the current reporting period (25 August 2022 to 24 February 2023), 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

Appendix 6.1 contains the methods used to calculate and perform the O/E analyses for the multiple sclerosis, including optic neuritis.

Since the previous PBRER DLP (24 August 2022), the broad O/E ratio has remained <1 in the US and EU for both age groups. A restricted O/E analysis with sensitivity analysis was therefore not required.

Results of the US and EU O/E analysis (broad) are provided in Appendix 6.2, this includes cumulative exposure, expected counts, and background incidence rates.

Conclusion

Based on the evaluation of the cases, and review of safety from other sources, the information retrieved during the reporting period remains consistent with previous observations regarding multiple sclerosis, including optic neuritis 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 cases of multiple sclerosis, including optic neuritis as an AESI.

16.3.6.2.3. Narcolepsy

Introduction

Narcolepsy is listed as an AESI in the cRMP, EU RMP, and the 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 period and cumulatively, which coded to the search criteria provided in Appendix 5.

An O/E analysis has been performed and information is presented in the O/E Analysis subsection below.

Results/Discussion

During this reporting period, a total of 24 (1 medically confirmed and 23 medically unconfirmed) initial, primary dose cases reporting narcolepsy were retrieved. There were 5 serious and 19 nonserious cases which reported a total of 24 EOI (3 serious, 21 nonserious).

During this reporting period, a total of 14 (2 medically confirmed and 12 medically unconfirmed) initial cases reported as booster were identified. There were 4 serious and 10 nonserious cases which reported a total of 14 EOI (2 serious, 12 nonserious). Of these cases, 9 were heterologous and 5 were homologous.

Post-marketing Sources (Including Spontaneous and Solicited) Cases

Primary Dose

During this reporting period, a total of 24 (1 medically confirmed and 23 medically unconfirmed) post-marketing, initial, primary dose cases reporting narcolepsy were retrieved. There were 5 serious and 19 nonserious cases which reported a total of 24 EOI (3 serious, 21 nonserious).

Cumulatively, 586 (79 medically confirmed and 507 medically unconfirmed) post-marketing, primary dose cases reporting narcolepsy were retrieved. There were 188 serious and 398 nonserious cases which reported a total of 594 EOI (94 serious, 500 nonserious).

An overview of these cases is presented in Table 66 below.

Table 66: Characteristics of Post-marketing Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Narcolepsy

Case Characteristics		Number of Cases Received During the Interval Reporting Period=24	Number of Cases Received Cumulatively=586[a]
Sex	Male	13	246
	Female	8	292
	NR	3	48
Age (Years)[b]	18 to 35	7	128
Minimum: 20	36 to 50	5	144
Maximum: 63	51 to 64	6	151
Mean: 40	Adult	1	6
Median: 40	NR	5	89
Source	Spontaneous	21	554

Table 66: Characteristics of Post-marketing Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Narcolepsy

Case Characteristics		Number of Cases Received During the Interval Reporting Period=24	Number of Cases Received Cumulatively=586[a]
	Clinical study (noninterventional, solicited)	3	32
Country/Territory	Germany	9	142
	Belgium	5	19
	United States	5	303
	Ghana	3	3
	Italy	1	4
	Norway	1	1
Event Characteristics		**Number of Events=24**	**Number of Events=594**
Seriousness (Event Level)[c]	Nonserious	21	500
	Serious	3	94
Outcome (Event Level)[c]	Resolving	7	68
	Not resolved	5	209
	Resolved with sequelae	4	11
	Resolved	3	122
	NR	5	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 period (25 August 2022 to 24 February 2023).

b: The median and mean age calculation were based on the current reporting period (25 August 2022 to 24 February 2023). 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 24 post-marketing primary dose cases received, the most frequently reported countries/territories of origin (n≥5) were Germany (n=9), and followed by Belgium and the US (n=5 each). These cases concerned 13 males, 8 females, and 3 did not report sex. The age range was from 20 to 63 years.

The frequency distribution of the MedDRA PTs of interest reported is presented in Table 67 below.

Table 67: 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 Interval Reporting Period[a]		Number of Events Reported Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
Sleep disorder	2	15	71	283
Hypersomnia	1	6	19	217

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: The MedDRA PTs of interest have been presented and sorted by decreasing order for the reporting period (25 August 2022 to 24 February 2023).
b: For the cumulative column, the events were presented in decreasing order based on the event counts of the current reporting period (25 August 2022 to 24 February 2023).

The EOI included sleep disorder (n=17) and hypersomnia (n=7). The mean and median TTO were 35.6 days and 1 day, respectively, and the range was from 0 to 426 days. Of the 24 EOI, outcomes were reported for 19 and are as follows: resolving (n=7), not resolved (n=5), resolved with sequelae (n=4), and resolved (n=3).

Booster Dose

During this reporting period, a total of 14 (2 medically confirmed and 12 medically unconfirmed) post-marketing, initial cases reported as booster were identified. There were 4 serious and 10 nonserious cases which reported a total of 14 EOI (2 serious, 12 nonserious). Of these cases, 9 were heterologous and 5 were homologous.

Cumulatively, 46 (5 medically confirmed and 41 medically unconfirmed) post-marketing cases reported as booster were identified. There were 15 serious and 31 nonserious cases which reported a total of 47 EOI (6 serious, 41 nonserious). Of these cases, 26 were heterologous and 20 were homologous.

An overview of these cases is presented in Table 68 below.

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

Case Characteristics		Number of Cases Received During the Interval Reporting Period=14	Number of Cases Received Cumulatively=46[a]
Sex	Female	7	28
	Male	5	14
	NR	2	4
Age (Years)[b]	18 to 35	2	10
Minimum: 26	36 to 50	3	14
Maximum: 84	51 to 64	5	13
Mean: 53.8	≥65	3	5
Median: 57	NR	1	4
Source	Spontaneous	9	38

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

Case Characteristics		Number of Cases Received During the Interval Reporting Period=14	Number of Cases Received Cumulatively=46[a]
	Clinical study (noninterventional, solicited)	5	8
Country/Territory	Germany	7	17
	United States	3	15
	Canada	2	3
	Brazil	1	5
	Italy	1	1
Classification	Heterologous	9	26
	Homologous	5	20
Event Characteristics		**Number of Events=14**	**Number of Events=47**
Seriousness (Event Level)[c]	Nonserious	12	41
	Serious	2	6
Outcome (Event Level)[c]	Resolving	4	7
	Resolved with sequelae	3	4
	Not resolved	2	17
	NR	5	13

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 period (25 August 2022 to 24 February 2023).

b: The median and mean age calculations were based on the current reporting period (25 August 2022 to 24 February 2023).

c: Seriousness and outcome have been presented for the EOI.

Of these 14 post-marketing cases reported as booster, the most frequently reported countries/territories of origin (n≥2) were Germany (n=7), the US (n=3) and Canada (n=2). These cases concerned 7 females, 5 males, and 2 did not report sex. The age range was from 26 to 84 years.

The frequency distribution of the MedDRA PTs of interest reported in post-marketing cases reported as booster is presented in Table 69 below.

Table 69: Frequency 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 Interval Reporting Period[a]		Number of Events Reported Cumulatively[b]	
	Serious	Nonserious	Serious	Nonserious
Sleep disorder	1	9	4	28
Hypersomnia	0	3	1	13
Narcolepsy	1	0	1	0

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: The MedDRA PTs of interest are sorted by decreasing order for the current reporting period (25 August 2022 to 24 February 2023).
b: For the cumulative column, the events were presented in decreasing order based on the event counts of the current reporting period (25 August 2022 to 24 February 2023).

The EOI included sleep disorder (n=10), hypersomnia (n=3), and narcolepsy (n=1). The mean and median TTO were 87.9 and 48 days, respectively, and the range was from 0 to 274 days. Of the 14 EOI, outcomes were reported for 9 and are as follows: resolving (n=4), resolved with sequelae (n=3), and not resolved (n=2).

Among 14 post-marketing cases, 1 heterologous booster case reported narcolepsy as an EOI. This was not a medically confirmed case and diagnosis of narcolepsy was not valid.

Clinical Trial Cases

During this reporting period, there were 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 period.

Line Listings

Death: During the current reporting period (25 August 2022 to 24 February 2023), no fatal cases were retrieved.

Booster: A cumulative CIOMS II LL of cases reported as booster is presented in Appendix 7.25.

O/E Analysis Results

Appendix 6.1 contains the methods used to calculate and perform the O/E analyses for the narcolepsy. Results of the restricted O/E and sensitivity analysis are presented in Table 70 below.

Table 70: 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 Count[a]	O/E Ratio (95% CI)[b] (PE, 100% RP)		O/E Ratio (95% CI)[b] (LB, 50% RP)	
EU	18 to 59	107.34	0.84	(0.69, 1.02)	3.23	(2.65, 3.91)
	≥60	21.62	2.97	(1.85, 4.51)	25.05	(15.63, 38.06)

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).

Results of the US and EU O/E analysis (both broad and restricted, where applicable) are provided in Appendix 6.2, this includes cumulative exposure, expected counts, and background incidence rates.

Conclusion

Based on the evaluation of the cases, and review of safety from other sources, the information retrieved during the reporting period 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 the US PVP.

Methods

The Company global safety database was searched for medically confirmed and medically unconfirmed cases received during this reporting period and cumulatively, which coded to the search criteria provided in Appendix 5.

An O/E analysis has been performed and information is presented in the O/E Analysis subsection below.

Results/Discussion

During this reporting period, a total of 152 (93 medically confirmed and 59 medically unconfirmed) initial, primary dose cases reporting cerebrovascular events were retrieved. There

were 151 serious and 1 nonserious case which reported a total of 199 cerebrovascular events (198 serious, 1 nonserious).

During this reporting period, a total of 26 (13 medically confirmed and 13 medically unconfirmed) initial cases reported as booster were identified. There were 24 serious and 2 nonserious cases which reported a total of 34 cerebrovascular events (32 serious, 2 nonserious). Of these cases, 7 were heterologous and 19 were homologous.

Post-marketing Sources (Including Spontaneous and Solicited) Cases

Primary Dose

During this reporting period, a total of 109 (50 medically confirmed and 59 medically unconfirmed) post-marketing, initial, primary dose cases reporting cerebrovascular events were retrieved. All these cases serious and reported a total of 152 serious cerebrovascular events.

Cumulatively, 1,622 (935 medically confirmed and 687 medically unconfirmed) post-marketing primary dose cases reporting cerebrovascular events were retrieved. There were 1,620 serious and 2 nonserious cases which reported a total of 2,235 cerebrovascular events (2,231 serious, 4 nonserious).

An overview of these cases is presented in Table 71 below.

Table 71: Characteristics of Post-marketing Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Cerebrovascular Events

Case Characteristics		Number of Cases Received During the Interval Reporting Period=109	Number of Cases Received Cumulatively=1,622[a]
Sex	Female	49	835
	Male	47	720
	NR	13	67
Age (Years)[b]	18 to 35	10	179
Minimum: 22	36 to 50	26	374
Maximum: 93	51 to 64	27	493
Mean: 53.7	≥65	19	415
Median: 52	NR	27	149
Sources	Spontaneous	107	1,602
	Clinical study (noninterventional, solicited)	2	20
Country/Territory	United States	66	1,093
	Germany	13	163
	Philippines	8	52
	South Africa	7	19
	Canada	2	2
	Ghana	2	2
	Italy	2	44
	Austria	1	11

Table 71: Characteristics of Post-marketing Primary Dose Cases Involving the Use of Ad26.COV2.S and Reporting Cerebrovascular Events

Case Characteristics		Number of Cases Received During the Interval Reporting Period=109	Number of Cases Received Cumulatively=1,622[a]
	France	1	44
	Greece	1	12
	Iran, Islamic Republic of	1	1
	Luxembourg	1	3
	Namibia	1	1
	Poland	1	23
	Romania	1	5
	Spain	1	19
Event Characteristics		**Number of Events=152**	**Number of Events=2,235**
Seriousness (Event Level)[c]	Serious	152	2,231
Outcome (Event Level)[c]	Not resolved	35	846
	Fatal	22	221
	Resolved	17	278
	Resolving	12	216
	Resolved with sequelae	1	39
	NR	65	635

Key: NR=Not Reported
a: For the cumulative column, the counts were presented in decreasing order based on the current reporting period (25 August 2022 to 24 February 2023).
b: The median and mean age calculation were based on the current reporting period (25 August 2022 to 24 February 2023).
c: Seriousness and outcome have been presented for the events of interest. A single case may report more than 1 event of interest.

Of these 109 cases received, the most frequently reported countries/territories of origin (n≥8) were the US (n=66), Germany (n=13), and the Philippines (n=8). These cases concerned 49 females, 47 males, and 13 did not report sex. The age range was from 22 to 93 years.

The frequency distribution of the serious MedDRA PTs of interest reported is presented in Table 72 below.

Table 72: 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 Interval Reporting Period[a]	Number of Serious Events Reported Cumulatively[b]
Cerebrovascular accident	50	671
Hemiparesis	16	192
Cerebral venous sinus thrombosis	11	151
Ischaemic stroke	7	111
Hemiplegia	6	81
Cerebral artery occlusion	5	25

Table 72: 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 Interval Reporting Period[a]	Number of Serious Events Reported Cumulatively[b]
Cerebral infarction	5	106
Transient ischaemic attack	5	138

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: The MedDRA PTs of interest with a frequency ≥5 have been presented and sorted by decreasing order for the reporting period (25 August 2022 to 24 February 2023). A single case may report more than 1 MedDRA PTs of interest.
b: For the cumulative column, the events were presented in decreasing order based on the event counts of the current reporting period (25 August 2022 to 24 February 2023).

The cerebrovascular events (≥11) included cerebrovascular accident (n=50), hemiparesis (n=16), and cerebral venous sinus thrombosis (n=11). The mean and median TTO were 136.7 days and 41 days respectively and the range was from the same day to 608 days. Of the 152 cerebrovascular events, outcomes were reported for 87 and are as follows: not resolved (n=35), fatal (n=22), resolved (n=17), resolving (n=12), and resolved with sequelae (n=1).

Information on Patients ≤40 Years of Age (Including Fatalities)

During this reporting period, a total of 2 fatal (1 primary dose and 1 case reported as booster) were reported in patients ≤40 years of age. In addition, a total of 18 non-fatal (17 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 7.26.1.

One booster case involved a fatal haemorrhagic event. Two of the non-fatal cases involved a haemorrhagic event (primary doses).

Both of the fatal cases reported a TTO within the 28-day risk window. Assessment of 1 of the cases (primary dose) was confounded by the patient's concurrent condition. The remaining case did not report medical history and/or concurrent disease that would confound the case, and included relevant details on medical history, concomitant medications, and diagnostic test results.

Of the 18 non-fatal cases, the EOI was outside the 28-day risk window in 6 cases (all primary dose). Of the remaining 12 cases, assessment in 5 (4 primary dose and 1 case reported as booster) were confounded by the patients' medical history and/or concurrent diseases. Of the remaining 7 cases, 7 (all primary dose cases) lacked relevant details, including TTO, medical history, concomitant medications, and diagnostic test results. Case information for the 18 non-fatal cases that occurred in patients ≤40 years of age are included in Appendix 7.26.1.

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

Booster Dose[18]

During this reporting period, a total of 25 (12 medically confirmed and 13 medically unconfirmed) initial cases reported as booster were identified. There were 24 serious and 1 nonserious case which reported a total of 33 cerebrovascular events (32 serious, 1 nonserious). Of these cases, 7 were heterologous and 18 were homologous.

Cumulatively, 66 (36 medically confirmed and 30 medically unconfirmed) cases reported as booster were identified. There were 65 serious cases and 1 nonserious case which reported a total of 86 cerebrovascular events (84 serious, 2 nonserious). Of these cases, 22 were heterologous and 44 were homologous.

An overview of these cases is presented in Table 73 below.

Table 73: Characteristics of Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Cerebrovascular Events

Case Characteristics		Number of Cases Received During the Interval Reporting Period=25	Number of Cases Received Cumulatively=66[a]
Sex	Male	11	35
	Female	11	28
	NR	3	3
Age (Years)[b]	18 to 35	2	7
Minimum: 23	36 to 50	4	14
Maximum: 92	51 to 64	7	21
Mean: 56.8	≥65	4	14
Median: 52	NR	8	10
Sources	Spontaneous	23	62
	Clinical study (noninterventional, unsolicited)	2	2
Country/Territory	United States	15	40
	Brazil	3	7
	Germany	3	10
	Greece	2	2
	Ireland	1	1
	South Africa	1	2
Classification	Homologous	18	44
	Heterologous	7	22

[18] After additional review of the case narrative and source article associated with AER [redacted], an error in the source article was identified in which Ad26.COV2.S was incorrectly characterised as an mRNA COVID-19 vaccine. This resulted in misinterpretation that 2 separate vaccines, Ad26.COV2.S and an mRNA COVID-19 vaccine, were administered and the case then being categorised as a booster case. Furthermore, the case processing team identified this case as a duplicate of AER [redacted] (initial AER approval date 12 August 2021), and case [redacted] has been deleted. The case details for AER [redacted] will be updated to remove an mRNA COVID-19 product as a suspect product and the change will be reflected in the next PBRER.

Table 73: Characteristics of Post-marketing Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Cerebrovascular Events

Case Characteristics		Number of Cases Received During the Interval Reporting Period=25	Number of Cases Received Cumulatively=66[a]
Event Characteristics		**Number of Events=33**	**Number of Events=86**
Seriousness (Event Level)[c]	Serious	32	84
	Nonserious	1	2
Outcome (Event Level)[c]	Fatal	6	13
	Not resolved	4	15
	Resolved	4	14
	Resolved with sequelae	1	4
	Resolving	1	7
	NR	17	33

Key: NR=Not Reported
a: For the cumulative column, the counts were presented in decreasing order based on the current reporting period (25 August 2022 to 24 February 2023).
b: The median and mean age calculations were based on the current reporting period (25 August 2022 to 24 February 2023).
c: Seriousness and outcome have been presented for the events of interest. A single case may report more than 1 event.

Of these 25 post-marketing cases reported as booster, the most frequently reported countries/territories of origin (n≥3) were the US (n=15), and followed by Brazil and Germany (n=3 each). These cases concerned 11 females, 11 males, and 3 did not report sex. The age range was from 23 to 92 years.

The frequency distribution of the MedDRA PTs of interest reported in post-marketing cases reported as booster is presented in Table 74 below.

Table 74: Frequency Distribution of MedDRA PTs of Interest in Cases Reported as Booster With the Use of Ad26.COV2.S and Reporting Cerebrovascular Events

MedDRA PTs	Number of Serious Events Reported During the Interval Reporting Period[a]	Number of Serious Events Reported Cumulatively[b]
Cerebrovascular accident	15	31
Hemiparesis	3	6
Ischaemic stroke	3	4
Transient ischaemic attack	3	6
Cerebral thrombosis	2	5

Key: MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
a: The MedDRA PTs of interest with a frequency ≥2 have been presented. The MedDRA PTs of interest are sorted by decreasing order for the current reporting period (25 August 2022 to 24 February 2023). 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 period (25 August 2022 to 24 February 2023).

The cerebrovascular events (n≥2) included cerebrovascular accident (n=15), hemiparesis, ischaemic stroke, and transient ischaemic attack (n=3 each), and cerebral thrombosis (n=2). The mean and median TTO were 137.4 days and 48 days respectively and the range is from same day to 419 days. Of the 33 cerebrovascular events, outcomes were reported for 16 and are as follows: fatal (n=6), not resolved and resolved (n=4 each) and resolved with sequelae and resolving (n=1 each).

Clinical Trial Cases

During this reporting period, a total of 44 clinical cases (43 primary dose and 1 booster) were retrieved from Janssen Sponsored and Janssen Supported Clinical Studies.

Janssen Sponsored Clinical Studies

During this reporting period, a total of 41 primary dose cases reporting cerebrovascular events were retrieved from Janssen Sponsored Clinical Studies. Of the 41 cases, 21 were from VAC31518COV3001 and 20 from VAC31518COV3009 These 41 cases reported 45 cerebrovascular events (44 serious, 1 nonserious). Of these 41 cases, the most frequently reported countries/territories (n≥9) of origin were the US (n=18) and Philippines (n=9). These cases concerned 23 males and 18 females. The age range was from 43 to 91 years.

The cerebrovascular events (n≥3) included cerebrovascular accident and ischaemic stroke (n=9 each), transient ischaemic attack (n=7), and cerebral infarction, and haemorrhagic stroke (n=3 each). The mean and median TTO were 527.8 and 540 days, respectively and the range was from 142 to 750 days. The outcomes were reported for all the 45 cerebrovascular events and are as follows: resolved (n=27), resolving (n=9), fatal(n=4), not resolved (n=3), and resolved with sequelae (n=2).

During this reporting period, 1 case reported as booster was identified from a Janssen Sponsored Clinical Study. This case was from VAC31518COV3009 and concerned a 60-year-old male from [redacted] This nonserious case reported 1 nonserious cerebrovascular event of cerebral infarction. The reported TTO was 609 days, and the event outcome was reported as resolving.

Janssen Supported Clinical Studies Cases

During this reporting period, a total of 2 primary dose cases reporting cerebrovascular events were retrieved from Janssen Supported Clinical Studies. Of the 2 cases, 1 was from [redacted] and the other from [redacted] These 2 cases reported 2 serious cerebrovascular events. The reported countries/territories of origin were [redacted] and [redacted] These cases concerned 1 male and 1 female. The reported age was 28 years and 71 years.

The cerebrovascular events included cerebrovascular accident and subarachnoid haemorrhage (n=1 each). The mean and median TTO were 158.5 days, and the range was from 34 to 283 days. The outcomes were reported as fatal and resolved (n=1 each).

There were no booster cases identified from Janssen Supported Clinical Studies.

Literature ICSR

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

Line Listings

Death: During the current reporting period (25 August 2022 to 24 February 2023), a total of 27 fatal cases were retrieved. Of these cases, 22 reported a fatal cerebrovascular event.

A CIOMS II LL of the fatal cases is presented in Appendix 7.26.2. Additional information on the fatal cases can also be found in Appendix 7.27, Death.

Booster: A cumulative CIOMS II LL of cases reported as booster is presented in Appendix 7.26.3.

O/E Analysis Results

Cerebrovascular Events - Haemorrhagic

Appendix 6.1 contains the methodology used to calculate and perform the O/E analyses for the cerebrovascular events.

Results of the restricted O/E and sensitivity analysis are presented in Table 75 below.

Table 75: Cerebrovascular Events - Haemorrhagic: Restricted O/E and Sensitivity Analysis Results (Cumulative Through 24 February 2023)

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	9.39	0.35	(0.16, 0.66)	3.07	(1.43, 5.76)
		30 to 39	13.58	0.37	(0.20, 0.63)	4.85	(2.63, 8.21)
		40 to 49	31.63	0.67	(0.46, 0.95)	10.85	(7.41, 15.35)
		50 to 64	62.28	0.43	(0.33, 0.56)	7.13	(5.47, 9.14)
		65 to 74	35.15	0.3	(0.21, 0.42)	3.31	(2.31, 4.60)
		≥75	32.29	0.2	(0.14, 0.29)	2.53	(1.73, 3.57)
	Male	18 to 29	1.66	0.03	(0.00, 0.14)	0.28	(0.02, 1.12)
		30 to 39	9.71	0.16	(0.08, 0.30)	1.99	(0.94, 3.70)
		40 to 49	20.87	0.28	(0.17, 0.43)	4.57	(2.83, 7.00)
		50 to 64	63.88	0.3	(0.23, 0.38)	4.63	(3.56, 5.91)
		65 to 74	31.12	0.2	(0.14, 0.28)	1.82	(1.24, 2.58)
		≥75	24.34	0.18	(0.11, 0.26)	2.43	(1.56, 3.61)
EU	Female	18 to 29	5.27	2.07	(0.70, 4.72)	11.73	(3.95, 26.81)
		30 to 39	2.21	0.6	(0.08, 2.06)	2.52	(0.36, 8.63)
		40 to 49	11.77	1.21	(0.62, 2.13)	3.69	(1.89, 6.49)
		50 to 64	13.81	0.41	(0.22, 0.69)	1.09	(0.59, 1.83)
	Male	18 to 29	6.00	2.03	(0.74, 4.41)	10.59	(3.89, 23.05)
		30 to 39	7.00	0.86	(0.35, 1.78)	2.86	(1.15, 5.89)
		40 to 49	4.44	0.27	(0.08, 0.67)	0.75	(0.22, 1.84)

Table 75: Cerebrovascular Events - Haemorrhagic: Restricted O/E and Sensitivity Analysis Results (Cumulative Through 24 February 2023)

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)**

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

Results of the restricted O/E and sensitivity analysis are presented in Table 76 below.

Table 76: Cerebrovascular Events – Non-Haemorrhagic: Restricted O/E and Sensitivity Analysis Results (Cumulative Through 24 February 2023)

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	10.67	0.29	(0.14, 0.51)	3.76	(1.85, 6.78)
		30 to 39	17.97	0.21	(0.12, 0.33)	4.33	(2.57, 6.85)
		40 to 49	42.07	0.32	(0.23, 0.43)	7.59	(5.47, 10.26)
		50 to 64	73.16	0.16	(0.12, 0.20)	4.59	(3.60, 5.77)
		65 to 74	38.54	0.09	(0.07, 0.13)	1.28	(0.91, 1.75)
		≥75	50.48	0.09	(0.07, 0.12)	1.13	(0.84, 1.48)
	Male	18 to 29	4.59	0.12	(0.04, 0.30)	1.35	(0.41, 3.27)
		30 to 39	13.63	0.12	(0.07, 0.21)	2.01	(1.09, 3.40)
		40 to 49	19.78	0.11	(0.07, 0.17)	1.99	(1.21, 3.08)
		50 to 64	86.67	0.13	(0.11, 0.17)	2.49	(2.00, 3.08)
		65 to 74	36.04	0.07	(0.05, 0.10)	0.8	(0.56, 1.11)
		≥75	26.30	0.06	(0.04, 0.09)	0.9	(0.59, 1.31)
EU	Female	18 to 29	6.27	0.67	(0.25, 1.45)	2.35	(0.88, 5.03)
		30 to 39	6.21	0.37	(0.14, 0.80)	1.05	(0.39, 2.25)
	Male	18 to 29	9.30	0.89	(0.41, 1.67)	3.05	(1.41, 5.72)
		30 to 39	13.23	0.79	(0.42, 1.34)	2.24	(1.20, 3.82)

Key: CI=Confidence Interval; EOI=Event(s) of Interest; EU=European Union; LB=Lower Bound; O/E=Observed versus Expected; PE=Point Estimate; RP=Reporting Percentage; US=United States
a: Counts included EOI (from valid cases) that occurred within the risk window (Day: 1 to 28) only.
b: Poisson exact confidence interval (95% CI).

The US restricted sensitivity analysis showed an O/E ratio of >1 for all female and all male age groups except the male 65 to 74 and ≥75 age groups. Of these, the O/E ratio was statistically significant above 1 (lower bound of 95% confidence interval >1) for all the female age groups except the 65 to 74 and the ≥75 age groups and for all the male age groups concerned except the 18 to 29 age group.

The EU restricted sensitivity analysis showed an O/E ratio of >1 for 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. Since the previous PBRER DLP (24 August 2022), for the EU female 30 to 39 age group, the restricted sensitivity O/E ratio showed an increase from <1 to >1. The O/E ratio was not statistically significant above 1 (lower bound of 95% confidence interval >1).

Results of the US and EU O/E analysis (both broad and restricted, where applicable) are provided in Appendix 6.2, this includes cumulative exposure, expected counts and background incidence rates.

Conclusion

During the reporting period, 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.

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 the fourth PBRER dated 25 August 2022 to 24 February 2023 and in future PBRERs. However, a separate subsection is found in Appendix 7.27 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 53,047,996 (CDC [2023], ECDC [2023], KDCA [2023]), 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 caused by SARS-COV-2 virus in adults ≥18 years of age.

16.4.1. Characterisation of Important Identified Risks

The current cRMP (version 6.0; dated 25 October 2022) was used as a reference for this section. VTE has been re-classified as an important identified risk. ITP is listed as an important potential risk in the current cRMP.

During the preparation of this report, the Company has finalised a cumulative evaluation on cardiac inflammatory disorders (myocarditis and pericarditis). Based on the available safety data, and the RWE analysis, the Company has concluded there is a reasonable possibility of a causal association. Myocarditis and pericarditis will be listed as an IIR (see Section 14, Late Breaking Information).

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-associated thromboembolic events with thrombocytopenia, including vaccine induction of platelet-activating antibodies directed against the cationic platelet chemokine PF4 (CXCL4), subsequently referred to as anti-PF4 antibodies (Greinacher 2021). Binding of Ad26 to PF4 has been suggested to trigger the coagulation cascade (Baker 2021). However, the Company could not confirm this interaction using several methodologies. Besides the adenovirus, a potential role of the S protein that has been associated with hypercoagulation, blood coagulation, and thrombosis in COVID-19 patients (Grobbelaar 2021, Zheng 2021), the inflammatory milieu as well as a predisposition of the patient should be considered.

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 ADR 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 or older.

In this cRMP, for purposes of TTS risk characterisation and presentation of cases, 3 case definitions are used: the interim 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:

TTS 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 thrombosis with thrombocytopenia syndrome 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:

GBS has been observed very rarely following vaccination with Ad26.COV2.S both in clinical trials, RWE 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.

GBS is an ADR described in the CCDS.

Characterisation of the Risk:

An update on the number of cases of GBS from clinical trial and post-marketing experience is provided in Section 16.3.1.2, Guillain-Barré Syndrome of this PBRER.

Risk Factors and Risk Groups:

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 of GBS signs and symptoms to ensure correct diagnosis, in order to initiate adequate supportive care and treatment and to rule out other causes.

Impact on the Risk-Benefit Balance of the Product:

Although GBS is a serious event that has been reported following vaccination with Ad26.COV2.S, it has been reported at a very low incidence and adequate risk minimisation via the CCDS is considered sufficient to manage this risk. Therefore, the impact on the risk-benefit balance for the vaccine is considered to be low.

Public Health Impact:

GBS associated with vaccines typically occurs at a low incidence, resulting in a low public health impact. Although the potential clinical consequences of GBS are serious, this is a risk known to healthcare professionals, with negligible public health impact.

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 S protein, as encoded by the vaccine, has been associated with hypercoagulation, blood coagulation, and thrombosis observed in COVID-19 patients (Grobbelaar 2021, Zheng 2021).

Recent mechanistic studies (nonclinical studies, and studies using clinical trial samples) conducted by the Company to study the pathogenesis of (vaccine-associated) TTS with potential relevance to VTE, did not 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:

VTE has been observed rarely following vaccination with Ad26.COV2.S in clinical trials and in the post-marketing setting. While a higher proportion of cases of VTE was observed within the Ad26.COV2.S group versus the placebo group in trial COV3001, there was no increase in VTE events among individuals who received Ad26.COV2.S in trial COV3009.

VTE 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 Warnings and Precautions) provides guidance to healthcare professionals to be alert to the signs and symptoms of thromboembolism.

Impact on the Risk-Benefit Balance of the Product:

VTE is a potentially life-threatening event, and if not recognised or managed appropriately, may result in persistent or significant disability or incapacity, and hence requires immediate medical intervention. Adequate risk minimisation via the CCDS is considered sufficient to manage this risk. Based on current information, the overall risk-benefit balance for Ad26.COV2.S is considered to remain positive for the indicated target populations.

Public Health Impact:

Based on the currently available information on the known frequency, clinical characteristics, and outcome of VTE events reported after Ad26.COV2.S vaccination, the public health impact is expected to be low.

16.4.2. Characterisation of Important Potential Risks

Important potential risks that may be associated with the use of Ad26.COV2.S include the following:

Vaccine-associated Enhanced Disease (VAED), Including Vaccine-associated Enhanced Respiratory Disease (VAERD)

Potential Mechanisms:

Potential mechanisms of enhanced disease may include both T cell-mediated immune responses (a Th2-skewed immune response favouring immunopathology) and antibody-mediated immune responses (antibody responses with insufficient neutralising activity leading to formation of immune complexes and activation of complement or allowing for Fc-mediated increase in viral entry to cells) (Graham 2020).

Evidence Source(s) and Strength of Evidence:

Based on past experiences in the development of vaccines against RSV, Dengue virus, SARS-CoV, and MERS-CoV, there is a theoretical risk for VAED, including VAERD, for SARS-CoV-2 vaccines (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 JCOVDEN 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 titres or in those demonstrating waning immunity (Graham 2020, Munoz 2020).

Preventability:

An effective vaccine against COVID-19 that produces strong humoral and cellular immune responses with a clear Th1 bias is expected to mitigate the risk of VAED, including VAERD (Lambert 2020, Graham 2020). Such an immune profile is elicited by Ad26.COV2.S in clinical trials and nonclinical studies.

Impact on the Risk-Benefit Balance of the Product:

A confirmed risk of VAED, including VAERD could significantly impact the risk-benefit balance of Ad26.COV2.S. The risk will be further characterised through follow-up of study 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.

Immune Thrombocytopenia

Potential Mechanisms:

The biological mechanism linking Ad26.COV2.S and ITP is not fully known. ITP has been reported in the past with other vaccines, especially live viral vaccines (Di Pietrantonj 2021). ITP has also been described following administration of other COVID-19 vaccines, including mRNA and adenovirus-based vaccines (Fueyo-Rodriguez 2021, Welsh 2021, Simpson 2021, Kuter 2021).

Although the exact mechanism of autoimmunity leading to ITP is still unclear, it is assumed that underlying mechanisms for ITP include an alteration of the balance between effector and regulatory immune cells. This imbalance results in a breakdown of the immune tolerance causing increased platelet clearance and impaired thrombopoiesis. Similar to other autoimmune disorders, molecular mimicry with bacterial or viral proteins might be one reason for the pathogenesis of ITP (Marini 2019).

The S protein, as encoded by the vaccine, has been associated with hypercoagulation, blood coagulation, and thrombosis observed in COVID-19 patients (Grobbelaar 2021, Zheng 2021).

Recent mechanistic studies (nonclinical studies, and studies using clinical trial samples) conducted by the Company to study the pathogenesis of (vaccine-associated) TTS with potential relevance to ITP, did not elucidate a clear mechanism of action for ITP following Ad26.COV2.S administration.

Evidence Source(s) and Strength of Evidence:

Very rare events of serious ITP (including fatal events) have been reported following vaccination with Ad26.COV2.S in clinical trials and in the post-marketing setting. Some of these events occurred in individuals with a history of ITP.

Characterisation of the Risk:

An update on the number of cases of ITP from clinical trial and post-marketing experience is provided in Section 16.3.2.2, Immune Thrombocytopenia of this PBRER.

ITP 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, including literature, with Ad26.COV2.S suggest that individuals with chronic or recurrent ITP may be at increased risk of developing ITP following vaccination with Ad26.COV2.S.

Preventability:

The CCDS (Section Warnings and Precautions) states that if an individual has a history of ITP, the risk of developing low platelet levels should be considered before vaccination, and platelet monitoring is recommended after vaccination.

Impact on the Risk-Benefit Balance of the Product:

ITP is a potentially life-threatening event, and if not recognised or managed appropriately, may result in persistent or significant disability or incapacity, and hence requires immediate medical intervention. ITP has been reported very rarely following vaccination with Ad26.COV2.S. Based on current clinical trial and post-marketing data and the information in the CCDS, the risk-benefit balance for the vaccine is considered to remain favourable for the indicated target populations.

Public Health Impact:

Based on the currently available information on the known frequency, clinical characteristics, and outcome of ITP events reported after Ad26.COV2.S vaccination, the public health impact is expected to be low.

16.4.3. Description of Missing Information

Use During Pregnancy

Evidence source:

There is 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 DLP of 24 February 2022, 23 women who were pregnant at baseline received at least one 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 DLP of 24 February 2022, 154 unique pregnancies were retrieved from Company-sponsored clinical trials post-baseline; 132 involved maternal exposure and 22 were partner pregnancies; all following Ad26.COV2.S administration. Overall, reported outcomes were live birth (n=10), spontaneous abortion (n=19), still birth (n=2), anembryonic pregnancy (n=1), ectopic pregnancy (n=1), elective abortion (n=4),

unknown (n=117). Of note, 1 participant reported 2 pregnancies during the trial (1 with an outcome of spontaneous abortion, 1 with an unknown outcome).

Up to the DLP of 24 February 2022, 461 unique cases reporting use in pregnancy were retrieved from post-marketing sources (including spontaneous and solicited cases); 460 involved maternal exposure and 1 was partner pregnancy. Of these unique pregnancy cases, 116 cases reported 119 outcomes due to 3 twin pregnancies: live birth without congenital anomaly (n=61 [including 1 set of twins]), spontaneous abortion (n=43 [including 2 sets of twins]), live birth with congenital anomaly (n=6), cases where congenital anomaly was detected with no birth outcome reported (n=4), ectopic pregnancy (n=3), and 1 case each of still birth without congenital anomaly and still birth with congenital anomaly. Of the 43 cases with outcome spontaneous abortion, there were 9 cases with exposure before conception, 22 cases with exposure during the first trimester of pregnancy, and for the remaining 10 cases 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 nonclinical 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 foetuses to date. Therefore, as stated in the CCDS (Section Pregnancy, Breastfeeding and Fertility), the administration of Ad26.COV2.S in pregnancy should only be considered when the potential benefits outweigh any potential risks to the mother and foetus.

A Phase 2 trial (COV2004) and a post-authorisation pregnancy exposure registry (COV4005) 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/use in breastfeeding women 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 Phase 3 trials COV3001, COV3003, and COV3009. Up to the DLP of 24 February 2022, 718 women who were breastfeeding at baseline have received at least 1 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 24 February 2022, there have been 122 unique cases (post-marketing spontaneous or non-interventional 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.

Breastfeeding women are being included in trials COV3001 and COV3009 to characterise the safety profile of Ad26.COV2.S in this subpopulation. A small subset of participants within trial COV2004 will be followed up during breastfeeding to assess the transfer of antibodies via breast milk. Breastfeeding women were also allowed to participate in trials COV2008 and COV3003.

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 Dec 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 Dec 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 1 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.

An update on the number of cases from clinical trial and post-marketing experience in immunocompromised patients is provided in Section 16.3.5.3, Use in Immunocompromised Patients of this PBRER.

Anticipated risk/consequence of the missing information:

Given the fact that Ad26.COV2.S is a replication-incompetent vaccine, the safety profile of Ad26.COV2.S when used in immunocompromised individuals is not expected to differ from that in the general population. 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 trials COV3001 and COV3009.

Use in immunocompromised patients will be further characterised in trial COV3018 and in the post-authorisation safety studies COV4003 and COV4001 and effectiveness studies COV4004 and COV4002.

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 enrolment 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 1 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 enroled. Of the 19,577 participants in the Per Protocol set who received Ad26.COV2.S ($5x10^{10}$ vp dose level), 6 (<0.1%) were defined as frail and 2,147 (11.0%) were defined as pre-frail. Of the 6 frail subjects, 5 (83.3%) were aged ≥60 years. Of the 2,147 pre-frail subjects, 1,338 (62.3%) subjects were aged ≥60 years (COV3001 CSR Dec 2021).

An update on the number of cases from clinical trial and post-marketing experience in frail patients with comorbidities is provided in Section 16.3.5.5, Use in Frail Patients With Comorbidities (eg, COPD, Diabetes, Chronic Neurological Disease, Cardiovascular Disorders) of this PBRER.

Population in need of further characterisation:

Safety data will be collected in individuals who are frail due to age or debilitating disease in trial COV3001, in the post-authorisation safety studies COV4003 and COV4001, in the post-authorisation effectiveness study COV4002, and through routine pharmacovigilance.

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) is ongoing.

An update on the number of cases from clinical trial and post-marketing experience in cases with interaction with other vaccines is provided in Section 16.3.5.6, Interactions with Other Vaccines of this PBRER.

Long-term Safety

Evidence source:

There are no available data on the long-term safety of Ad26.COV2.S.

Based on long-term safety data from other Ad26-based vaccines (at least 6 months up to 5 years post-vaccination in clinical trials), no long-term safety issues have been identified (Adenoviral Vaccine Safety Database V7.0 2022).

An update on the number of long-term safety cases is provided in Section 16.3.5.7 of this PBRER.

Population in need of further characterisation:

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 ongoing trials COV3001 and COV3009 following administration of Ad26.COV2.S, and for up to 1 year in the post-authorisation safety studies COV4003 and COV4001.

Participants of trials COV3001 and 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 US 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 enrolment into study.

16.5. Effectiveness of Risk Minimisation

No significant new information on the effectiveness or limitations of specific risk minimisation activities for the important identified risk or important potential risk has become available during the reporting period for Ad26.COV2.S.

Direct Healthcare Professional Communications (DHCP) have been fully implemented globally and the content related to the risk of TTS is appropriately mitigated through routine risk minimisation measures.

Additionally, all DHPCs have been fully retired at the end of the reporting period with the approval of EU RMP version 5.3 as well as the cRMP version 6.0.

17. BENEFIT EVALUATION

As of 06 April 2023, there have been 762,201,169 confirmed cases of COVID-19 globally, including 6,893,190 deaths. As of 04 April 2023, over 13.3 billion vaccine doses have been administered. (WHO 2023a). In Europe, as of 4 April 2023, there have been a total of 275,962,10 confirmed cases of COVID-19, and 2,213,394 cases of COVID-19 related deaths (WHO 2023b).

In the US, as of 06 April 2023, there have been a total of 104,242,889 confirmed cases of COVID-19 reported, and 1,127,104 cases of COVID-19 related deaths reported. A total of 674,375,206 vaccine doses have been administered. (CDC 2023)

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.1.5 being classified as a VOI on 11 January 2023, a number of other Omicron sublineages are designated as VUMs as of 30 March 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 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 and COV3009), 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 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 (heterologous boost only), compared with pre-boost timepoint This translates into an increased vaccine effectiveness against COVID-19 related infections, hospitalisations, and deaths after Ad26.COV2.S boosting, including during the Omicron-emerging and Omicron-predominant periods, as shown in RWE studies.

17.3. Characterisation of Benefits

With the disease burden of COVID-19 remaining high, a COVID-19 vaccine that can easily be administered in a regimen that elicits long-term high protection against symptomatic COVID-19 is needed. Protection against severe/critical disease and in older/fragile age groups and other populations at high risk will reduce the burden on health care systems by lowering COVID-19 related hospitalisations/deaths. Also, protection with a similar magnitude against existing and (newly) emerging SARS-CoV-2 variants, will be of high value to continue fighting the COVID-19 pandemic.

18. INTEGRATED BENEFIT-RISK ANALYSIS FOR APPROVED INDICATIONS

18.1. Benefit-Risk Context – Medical Need and Important Alternatives

Medical Need

On 11 March 2020, the WHO characterised the COVID-19 outbreak as a pandemic. In response to the public health emergency, the EMA pandemic Task Force was formed from 31 March 2020 (EMA 2020a). The Ad26.COV2.S prophylactic vaccine programme is an accelerated development programme that was designed specifically to address the COVID-19 pandemic. Despite the present availability of currently authorised vaccines, and the prevalence of natural infections, herd immunity has not yet been achieved, and travel from countries with a higher incidence of infection as well as the emergence of new variants means that the potential for new outbreaks is still a significant concern. The risk of outbreaks and emergence of new variants highlights the need to continue primary vaccination. A 1-dose regimen and favourable storage conditions are advantages conferred by the Ad26.COV2.S vaccine in protecting against COVID-19 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 06 April 2023, there have been 762,201,169 confirmed cases of COVID-19, including 6,893,190 deaths worldwide (WHO 2023a). In Europe, as of 4 April 2023, there have been a total of 275,962,10 confirmed cases of COVID-19, and 2,213,394 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 preexisting conditions, and severity of illness and significantly varies between countries (Cascella 2022). Therefore, while the understanding of the epidemiology and clinical spectrum of COVID-19 is still evolving, the disease burden continues mounting.

18.2. Benefit-risk Analysis Evaluation

Key Benefits

The SARS-CoV-2 outbreak constitutes a public health emergency of international concern. The ongoing COVID-19 pandemic has already caused over 6.9 million deaths worldwide and continues to devastate lives. Effective and safe COVID-19 vaccines that can be easily administered are pivotal in ending this pandemic. Therefore, the MAH has evaluated efficacy, immunogenicity, and

safety of a 1-dose COVID-19 vaccine, Ad26.COV2.S, in an ethnically and geographically diverse adult population.

Key Efficacy Data From Phase 3 Studies and RWE

Previously submitted results from single dose study COV3001 and homologous booster study COV3009 indicated that administration of a homologous booster 2 months after primary vaccination with Ad26.COV2.S increased the point estimates of VE against symptomatic and severe/critical COVID-19, including against SARS-CoV-2 variants with sufficient cases for analysis, based on a 1-month median follow-up after the booster vaccination.

Efficacy data from these Phase 3 studies have shown that vaccination with Ad26.COV2.S also shows a level of protection against any SARS-CoV-2 infections (both symptomatic and asymptomatic infections combined), with higher VE point estimates after a homologous booster. Although VE (95% CI) against asymptomatic SARS-CoV-2 infections was generally low after single dose vaccination in COV3001 (28.9% [19.99; 36.78]), a country specific subgroup analysis for the US has shown a VE (95% CI) of 58.8% (44.69; 69.54) when evaluated at least 28 days after vaccination, confirming that VE always needs to be interpreted in view of emerging SARS-CoV-2 variants, including VOCs/VOIs, with varying levels protection against these. Furthermore, in case of breakthrough infections, a reduction in severity, duration, and symptoms of COVID-19 and a reduction in viral load was observed, potentially reducing the risk of transmission. This shift to lower COVID-19 severity may additionally explain the generally low VE estimates against asymptomatic SARS-CoV-2 infections compared with the higher VE estimates against more severe COVID-19.

Furthermore, recently published data from SISONKE 2 and other RWE studies confirm the benefit of a homologous or heterologous Ad26.COV2.S booster dose in protecting against COVID-19 related infections, hospitalisations, and deaths, also during the Omicron-emerging and Omicron predominant periods.

Supporting Immunogenicity Data

Previously submitted results from studies COV1001, COV1002, COV2001, and COV3009 have shown that a homologous booster dose of Ad26.COV2.S (5×10^{10} vp), either 2 or 3 months after the first vaccination, induced an increase in humoral immune responses, which were durable up to at least 4 to 6 months after booster vaccination. These data are consistent with the homologous Ad26.COV2.S booster data from the Mix and Match Study DMID 21-0012, in which the booster was administered >12 weeks after primary vaccination. In addition, a homologous Ad26.COV2.S booster, administered 2 or 3 months after primary vaccination in adults ≥18 years of age, elicited cellular responses that persisted up to at least 6 months after boosting. These data further support the durability of the immune responses elicited by a homologous Ad26.COV2.S booster.

Data from the primary analysis of COV2008 Cohort 1 have demonstrated NI of neutralising antibody 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. 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.

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 ≥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.

The safety concerns from the EU RMP (version 5.3, dated 13 February 2023) in place at the end of the renewal reporting period are presented in Section 16.1.2, Summary of Safety Concerns at the End of the Reporting Period.

Key Risks

The safety concerns from the current cRMP (version 6.0; dated 25 October 2022) are provided in Table 77 below:

Table 77: Safety Concerns at the End of the Reporting Period

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

Key: ITP=Immune thrombocytopenia
a: ITP is characterised in the European Union Risk Management Plan version 5.3 as Important Identified Risk "Thrombocytopenia, including ITP".

During the preparation of this report, the Company has finalised a cumulative evaluation on cardiac inflammatory disorders (myocarditis and pericarditis). Based on the available safety data, the Company has concluded there is a reasonable possibility of a causal association. Myocarditis and pericarditis will be listed as an IIR (see Section 14, Late Breaking Information).

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 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.

As previously indicated above, myocarditis and pericarditis will be listed as an IIR (see Section 14, Late-Breaking Information).

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 28 February 2023, over 53,047,996 doses of the Ad26.COV2.S 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.

Based on the newly published estimates of Janssen vaccine primary and booster doses duration of effectiveness during Omicron predominance, Janssen COVID-19 vaccine continues to provide protection during Omicron predominance. The newly identified risk of myocarditis and pericarditis does not change the existing established benefit/risk profile. The MAH will continue to monitor the benefit-risk profile of Ad26.COV2.S as Omicron predominance wanes and when other variants, perhaps with different transmission intensity and severity characteristics, are circulating.

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.

19. CONCLUSIONS AND ACTIONS

During the period of this update including late-breaking information, myocarditis and pericarditis have been considered ADRs and IIRs associated with Ad26.COV2.S. Consequently, an update to the safety sections of the prescribing information as well as risk management plan will be implemented accordingly. 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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